6.1.4 If in a country of the Territory where there is a Patent in force and/or Data Exclusivity applies and one or more third parties (other than Affiliates or Business Partners of Janssen) sell pharmaceutical products containing Synaptech Analogues which compete directly with the Licensed Product and such competing products take more than 20% by value of sales of the Licensed Product in that country for two consecutive Quarters then in respect of that country only the Secondary Royalty Rate shall apply instead of the Primary Royalty Rate for as long as such competing products take more than 20% by value of sales of the Licensed Product in that country.

6.1.5 If in a country of the Territory where there is no Patent in force and Data Exclusivity does not apply and one or more third parties (other than Affiliates or Business Partners of Janssen) sell pharmaceutical products containing Galanthamine or Synaptech Analogues which compete directly with the Licensed Product and such competing products take more than 20% by value of the Licensed Product in that country for two consecutive Quarters then in respect of that country only the Tertiary Royalty Rate shall apply instead of the Secondary Royalty Rate for as long as such competing products take more than 20% by value of sales of the Licensed Product in that country.

6.1.6 For the avoidance of doubt the royalty rate reductions referred to in Clauses 6.1.4 and 6.1.5 above shall apply in respect of the first Quarter in which the competing products take more than 20% by value of sales of the Licensed Product in the country concerned. In succeeding Quarters the Secondary Royalty Rate (in the case of Clause 6.1.4) or the Tertiary Royalty Rate (in the case of 6.1.5) shall apply until a Quarter is reached when such competing products no longer take more than 20% by value of sales of the Licensed Product in the relevant country in which case the Secondary Royalty Rate (in the case of Clause 6.1.4) or the Tertiary Royalty Rate (in the case of Clause 6.1.5) shall apply to that Quarter but the Primary Royalty Rate (in the Case of Clause 6.1.4) or the Secondary Royalty Rate (in the case of Clause 6.1.5) shall apply to succeeding Quarters.

6.1.7 The Primary Royalty Rate, the Secondary Royalty Rate and the Tertiary Royalty Rate shall vary according to the Average Cost of Galanthamine Raw Material as follows :-

6.1.7.1 For countries within the Shire Territory:-

Average Cost of Galanthamine Raw Material per kilogram in pounds sterling	Primary Royalty Rate	Secondary Royalty Rate	Tertiary Royalty Rate
5,000 or more	8%	5%	2%
4,000-4,999.99	8.5%	5.5%	2.5%
3,000-3,999.99	9%	6%	3%
2,000-2,999.99	9.5%	6.5%	3.5%
less than 2,000	10%	7%	4%

6.1.7.2 For countries within the Janssen Territory:-

Average Cost of Galanthamine Raw Material per kilogram in pounds sterling	Primary Royalty Rate	Secondary Royalty Rate	Tertiary Royalty Rate
5,000 or more	9%	6%	3%
4,000-4,999.99	9.5%	6.5%	3.5%
3,000-3,999.99	10%	7%	4%
2,000-2,999.99	10.5%	7.5%	4.5%
less than 2,000	11%	8%	5%

6.1.8 For the purposes of Clause 6.1.7 only, the Average Cost of Galanthamine Ra Material shall be whichever is the lower of:-

6.1.8.1 the average purchase price paid by Janssen or its Affiliates to Shire or third party (other than an Affiliate of Janssen) for commercial stocks Galanthamine Raw Material taken over the previous four Quarters. the Galanthamine Raw Material concerned is Natural Galanthamine th the average purchase price shall exclude the cost of purchasing the pla bulb material.

6.1.8.2 the average purchase price (excluding VAT, and other sales taxes an duties, freight, insurance, packaging and other indirect costs of suppl paid by Shire or its Affiliates to Janssen or its Affiliates for commerci stocks of Galanthamine Raw Material in accordance with Clause 16.3.2 taken over the previous four Quarters. If Finished Product is suppli instead of Galanthamine Raw Material then the Average Cost of Galanthamine shall be calculated by deducting Janssen or its Affiliat Standard Cost of converting Galanthamine Raw Material into Finish Product from the purchase price paid by Shire or its Affiliates fo Finished Product.

6.1.8.3 the price at which a third party offers to supply commercial stocks Galanthamine Raw Material (excluding VAT and other sales tax duties, freights, insurance and packaging) provided that su Galanthamine Raw Material (1) meets all necessary standards to enal it to be used in the United States of America and the Europe Community and (2) can be supplied in sufficient quantity to meet t requirements of any Major Country.

6.1.8.4 Janssen or its Affiliates Standard Cost of Galanthamine Raw Mater plus the 5% fee as provided in Clause 16.3.2.

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6.1.9 If in Clause 6.1.8 the figures for the cost of Galanthamine Raw Material for the previous four Quarters' are not available then the Average Cost of Galanthamine Raw Material shall be calculated over such previous Quarters for which figures are available.

6.1.10 With respect to any Standard Cost referred to in this Agreement, each party shall have the right to appoint an independent auditor to inspect the records and books of account of the producer for the purpose of verifying that the Standard Cost has been calculated in accordance with the provisions of Clause 1.41. The parties shall procure that the auditor is given all reasonable assistance and access when carrying out such inspection. Any dispute concerning the Standard Cost shall be referred to an expert pursuant to Clause 28.13.

6.1.11 Royalties payable under this Clause 6.1 are subject to the apportionment (if any) of Net sales Value in accordance with the provisions of Clause 8.3.

6.1.12 For the avoidance of doubt in no circumstances shall Janssen be obliged to pay a royalty under both Clause 6.1.2 and Clause 6.1.3 in respect of the same sales of Licensed Product in any country within the Territory.

6.2 Frequency of Payment

Royalties due under this Clause 6 shall be payable within 45 days of the end of each Quarter in respect of sales of the Licensed Product made during such Quarter.

6.3 Combination Products

Janssen and its Affiliates shall not sell the Licensed Product in combination with any other compound, materials, equipment or apparatus without the parties having first agreed upon what proportion of the total selling price of the combination product should be attributable to the Licensed Product. The parties shall in each case use their reasonable endeavours to negotiate in good faith a fair and reasonable proportion. If the parties fail to agree a proportion within 90 days then either party shall be entitled to refer the matter to an expert for resolution pursuant to Clause 28.13.

6.4 Supplies which are not made on an "arms length" basis

6.4.1 If Janssen, its Affiliates or Business Partners sell the Licensed Product to any Customer other than on an "arm's length" commercial basis, the Net Sales Value of such Licensed Product shall be which ever is the higher of:-

6.4.1.1 the fair market value of such Licensed Products; or

6.4.1.2 the actual price at which Janssen, its Affiliate or Business Partner sold the Licensed Products to such Customer.

6.4.2 If Janssen, its Affiliates or Business Partners supply the Licensed Product to any Customer as part of package of products or services then the Net Sales Value of the Licensed Product shall be which ever is the higher of:-

6.4.2.1 the fair market value of the Licensed Product when sold by itself; or

6.4.2.2 the proportion of the package price attributed to the Licensed Product by (1) Janssen its Affiliate or Business Partner and (2) the Customer.

6.4.3 This Clause 6.4 shall be without prejudice to the right of Janssen, its Affiliates and Business Partners to offer ordinary trade discounts in accordance with their normal business practices.

6.4.4. For the purposes of this Clause 6.4, fair market value shall mean, without limitation, the value of Licensed Product sold to similar Customers in countries with similar pricing and reimbursement structures and for similar quantities. Any dispute as to the determination of fair market value that cannot be resolved through discussion between the parties shall be referred to an expert for resolution pursuant to Clause 28.13.

6.5 Compulsory Licenses

If a compulsory licence is granted in respect of the Manufacturing Patents:-

6.5.1 in any country of the Territory then the parties shall share any royalty payments or other payments paid under such granted compulsory licence (after deduction of any sums payable to Synaptech in respect of such granted compulsory licence) in the proportion one-third to Shire and two-thirds to Janssen;

6.5.2 in the United Kingdom and/or the Republic of Ireland then any royalty means or other payments paid under such granted compulsory licence (after deduction of any sums payable to Synaptech in respect of such granted compulsory licence) shall be included in the UK and Ireland Sales Account to be shared between the parties in accordance with the provisions of Clause 10;.

6.5.3 in any country of the Excluded Territory (other than the United Kingdom and the Republic of Ireland) then any royalty payments or other payments paid under such granted compulsory licence (after deduction of any sums payable to Synaptech in respect of such granted compulsory licence) shall be retained in full by Shire.

7. PAYMENT TERMS

7.1 All sums due under this Agreement:-

7.1.1 Are exclusive of any Value Added Tax, or other sales taxes or duties which where applicable will be payable by Janssen to Shire in addition.

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7.1.2 Shall be made in pounds sterling to the credit of a bank account to be designated in writing by Shire. If the Licensed Product is sold or supplied by Janssen or its Affiliates in a currency other than pounds sterling the Net Sales Value shall first be determined in the currency in which such Licensed Product was sold or supplied and then converted into equivalent pounds sterling at the middle market rate of such foreign currency as quoted by the in London Financial Times as at the close of business of the last business day of the Quarter with respect to which the payment is made.

7.1.3 Shall be made in full without deduction or income or other taxes, charges and/or duties that may be imposed except insofar as Janssen is required to deduct the same to comply with relevant laws. In the event that Janssen is required to make any such deduction it shall promptly provide Shire with a certificate or other documentary evidence sufficient to enable Shire to support a claim for a tax credit in respect of any amount so withheld.

7.1.4 If Shire cannot take a full credit against its tax liability for the withholding tax deducted or withheld by Janssen then the parties shall use reasonable endeavours to agree a change to the then current arrangement with respect to the flow of monies under this Agreement in order to reduce or eliminate the loss to Shire. This clause 7.1.4:-

7.1.4.1 shall not be applicable if Shire cannot take a full credit against its tax liability for the withholding tax due to Shire's negligence in failing to comply with all legal and other requirements necessary to claim such tax credit;

7.1.4.2 shall not require Janssen to compensate Shire for the proportion of the withholding tax against which Shire is unable to obtain a tax credit; and

7.1.4.3 shall also apply to all payments made to Shire under the Shire-Janssen Sub-licence Agreement.

7.1.5 Shall be made by the due date for payment as provided in this Agreement failing which Shire may without prejudice to any other right or remedy available to Shire under this Agreement, charge interest on any outstanding amount overdue for 14 days on a daily basis at a rate equivalent to LIBOR (6 months) plus two per cent.

7.2 Prohibitions on Payment

7.2.1 If Janssen is prohibited from making any of the payments required hereunder by a governmental authority then Janssen will within the prescribed period for making the said payments in the appropriate manner use its reasonable endeavours to secure from the proper authority in the relevant country permission to make the said payments and will make them within 30 days of receiving such permission.

7.2.2 In the event that such permission is not received within thirty (30) days of Janssen making such a request for permission, then at the option of Shire, Janssen shall deposit the royalty payments due either in a bank account designated by Shire within the relevant country, or such royalty payments shall be made to an Affiliate of Shire designated by Shire and having offices in the relevant country.

8. Records And Reports

8.1 Maintain Records

8.1.1 Janssen, its Affiliates and Business Partners shall keep at their normal place of business detailed, accurate and up to date records and books of account showing the quantity, description and value of the Licensed Products supplied by Janssen, its Affiliates and Business Partners in each country within the Territory during the previous two years and being sufficient to ascertain the royalties payable during the term of this Agreement and for one year thereafter.

8.1.2 Having been given ten or more days notice by Shire, Janssen shall make such records and books available for inspection at all reasonable times during business hours not more than twice in any calendar year by Shire or an independent auditor appointed by Shire for the purpose of verifying the accuracy of any statement or report given by Janssen to Shire and/or the amount of royalties due and any such representatives making such inspection shall be entitled to take copies or extracts from the records and books of account of Janssen, its Affiliates and Business Partners. In the case of Business Partners, Janssen shall procure that the Business Partners deliver the relevant part of their records and books of account to Janssen's premises and inspection shall take place at Janssen's premises.

8.1.3 Shire and its independent auditor appointed under Clause 8.1.2 above shall maintain all such information and materials in strict confidence save where Shire has recording and reporting obligations under its agreements with third parties relating to the subject matter of this Agreement in which case Shire shall use reasonable endeavours to procure that such third parties maintain such information and materials in strict confidence.

8.1.4 Shire shall be solely responsible for its costs in making such inspections unless there is a material inaccuracy that is an inaccuracy greater than 5 per cent on any royalty statement in which event Janssen shall forthwith pay to Shire the costs in making the relevant inspections make good the deficit and pay interest on the deficit at LIBOR (6 months) plus two per cent.

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8.2 Royalty Statements

Janssen shall send to Shire at the same time as each royalty payment is made under Clause 6.2 above a statement:-

8.2.1 setting out in respect of each country in which Licensed Product is supplied to a Customer, by presentation form, the quantity and Net Sales Value of Licensed Products sold or supplied free of charge during the Quarter to which the royalty payment relates. The Statement shall show the total Net Sales Value for each country expressed both in local currency and in pounds sterling, showing the conversion rate used; and

8.2.2 showing for each country in which the Licensed Products are sold, the applicable royalty rate used and the calculation of the royalties payable pursuant to Clause 6.1.

8.3 Apportionment of Net Sales Value between Alzheimer's disease and Chronic Fatigue Syndrome

Janssen and Shire are aware that if they co-develop Galanthamine for use in the treatment of CFS as envisaged in Clause 17 a difficulty will exist throughout the Territory in determining whether Galanthamine has been used for the treatment of Alzheimer's disease and related dementias or for the treatment of CFS. Janssen and Shire have, in agreement with Synaptech, determined to resolve this problem in the Territory in the following manner:-

8.3.1. Janssen will make reasonable efforts to report to Shire for each country of the Territory sales of Galanthamine for (1) Alzheimer's disease and related dementias and (2) CFS and shall report the same on a confidential basis on the first day of January and the first day of July in each year within 60 days of each such date in each year.

8.3.2 In any country of the Territory where only one of either (1) the Licensed Product has been granted a Product Approval ("Alzheimer's Approval") or (2) where all necessary government or regulatory authority (including without limitation acceptable pricing and reimbursement) to sell Galanthamine for the treatment of CFS has been granted ("CFS Approval") then all sales of Galanthamine in that country of the Territory shall be attributed to either (1) Licensed Product if Alzheimer's Approval has been obtained or (2) CFS if CFS Approval has been obtained. Upon the date that both Alzheimer's Approval and CFS Approval have been granted in a country of the Territory then Clause 8.3.3 below shall apply in respect of such country.

8.3.3. Janssen and Shire agree that to establish the percentage proportion of sales of Galanthamine in any country of the Territory for the purpose of calculating royalty payments applicable to Synaptech for Alzheimer's disease and related dementias and to the third party holder of patent rights covering the use of Galanthamine in the treatment of CFS ("the proportion"), patients of the age of 50 and over shall be deemed to have Alzheimer's disease and related dementias and patients under 50 years shall be deemed to have CFS.

8.3.4 If either party reasonably believes that a more accurate method of reporting under Clause 8.3.1 and calculation of the proportion set out in Clause 8.3.3 has become available it will consult with the other in an effort to amend this clause appropriately in consultation with Synaptech. If no agreement can be reached within 6 weeks then either party shall have the right by serving notice in writing on the other to refer the matter for resolution pursuant to Clause 28.12. Notwithstanding the foregoing no change to the method of calculation of the proportion set out in Clause 8.3.3 shall be made unless such change has been agreed by both Synaptech and the third party holder of patent rights covering the use of Galanthamine for the treatment of CFS.

8.3.5 With regard to an individual sale of Galanthamine in the Territory by Janssen or an Affiliate or Business Partner of Janssen, Janssen shall pay a royalty on such sale on the basis that either (1) the Galanthamine will be used for the treatment of Alzheimer's disease and related dementias or (2) that it will be used for the treatment of CFS. In no circumstances shall Janssen be required to pay royalties on an individual sale of Galanthamine in respect of both Alzheimer's disease and CFS.

9. Janssen's Development, Launch And Marketing Efforts

9.1 Janssen's Reasonable Efforts

Where in this Clause 9 Janssen is required to use reasonable efforts consistent with its normal business practices such level of effort will be consistent with the level of effort used by Janssen in connection with other products of Janssen of similar importance which Janssen intends to launch and sell worldwide (based on such criteria as patient population, price per treatment and competitive position).

9.2 Janssen's Development and Product Approval Filing Efforts

9.2.1 Janssen shall supply Shire at least once every Quarter with a report on the status of the development of the Licensed Product.

9.2.2 Janssen shall use reasonable efforts consistent with its normal business practices to carry out the development activities directed to the Licensed Product with the aim of developing Licensed Product that can be commercialised.

9.2.3 In view of the competitive market position in connection with second generation cholinesterase inhibitors the parties have agreed on the requirement for an aggressive development timetable as set out in the Co-Development Plan. Therefore, if Janssen and its Affiliates do not reasonably pursue the development of the Licensed Product and as a consequence thereof incur a delay of more than 4 months on the timetable set out in the Co-Development Plan, excluding any delay caused by reasons beyond the reasonable control of Janssen and its Affiliates, Shire may notify Janssen of such delay. After receiving such notice Janssen shall take immediate action to rectify its efforts so as to comply with the timetable set out in the Co-Development Plan.

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9.2.4 Consistent with the competitive market position as described in Clause 9.2.3 above, Janssen shall use reasonable efforts consistent with its normal business practices to file and procure the grant of applications for Product Approval in the Major Countries as quickly as possible. In any event Janssen shall file the Product Approval applications in accordance with the target dates set out in Schedule 2 provided that Janssen shall not be in breach of its obligations under this Clause 9.2.4 if it fails to file any application for Product Approval in accordance with such target dates due to circumstances beyond the reasonable control of Janssen and its Affiliates.

9.2.5 If in any Major Country, Product Approval is not granted within 12 months of having applied for such Product Approval then the parties shall promptly discuss potential courses of action to obtain the grant of such Product Approval.

9.3 Janssen's Launching and Marketing Efforts

9.3.1 Subject to the provisions of Clauses 9.2, 9.3.3 and 9.3.6 all business decisions, including but not limited to, pricing, reimbursement, package design, sales and promotional activities relating to the Licensed Product in the Territory, shall be within the sole discretion of Janssen.

9.3.2 Janssen, its Affiliates and/or Business Partners as the case may be, shall be solely responsible for the preparation of scientific literature and promotional material relating to Licensed Product in accordance with its normal business practices and quality standards. A copy of any such scientific and/or promotional material shall be supplied to Shire free of charge upon Shire's request.

9.3.3 Janssen shall use reasonable efforts consistent with its normal business practices to launch the Licensed Product in each Major Country within six (6) months after obtaining Product Approval in such Major Country. Such six (6) month period shall be extended for such period as Janssen may reasonably request for sound business reasons consistent with the competitive market position as described in Clause 9.2.3 above provided that any such requested extension shall not exceed a period of four months.

9.3.4 Janssen shall promptly inform Shire of the date of launch of the Licensed Product in each of the Major Countries and shall regularly update Shire on the launch of the Licensed Product in other countries.

9.3.5 Janssen shall submit for Shire's consideration a copy of a global plan for the marketing and the sale of Licensed Product in Territory and will do so not less than 120 days prior to the first Commercial Delivery in any Major Country. Such global plan will be annually updated by Janssen and a copy thereof will be promptly sent to Shire. Subject to Janssen's ultimate decision rights as set forth in Clause 9.3.1, Shire may send comments to Janssen on such plan(s) for Janssen's consideration. Such plan(s) will be treated by Shire as strictly confidential and will not be disclosed to any third party without the prior approval of Janssen.

9.3.6 Janssen shall use reasonable efforts consistent with its normal business practices to promote and market the Licensed Product in each Major Country after launch in such Major Country.

10 Co-Promotion in the United Kingdom and the Republic of Ireland

Janssen and Shire shall procure that their respective Affiliates in the United Kingdom and the Republic of Ireland co-promote the Licensed Product in the United Kingdom and Republic of Ireland by reference to the Trade Marks on and subject to the provisions set out in this Clause 10 and enter into a detailed co-promotion agreement prior to the filing of Product Approval covering the United Kingdom and the Republic of Ireland. Such co-promotion agreement shall without limitation include provisions equivalent to those set out below:-

10.1 Shire or its Affiliates shall apply for and hold the Product Approvals for the United Kingdom and the Republic of Ireland. Shire shall be primarily responsible for the promotion and marketing of the Licensed Products in the United Kingdom and the Republic of Ireland and Janssen shall provide Shire with such support as Shire may reasonably request.

10.2 Janssen and its Affiliates shall use reasonable endeavours to procure on behalf of Shire sales of the Licensed Product in the United Kingdom and the Republic of Ireland. Shire shall fulfil all orders for the Licensed Product procured by Janssen and its Affiliates sales representatives in the United Kingdom and the Republic of Ireland and receive the purchase price paid in respect of such orders.

10.3 Shire shall maintain all receipts generated from sales of the Licensed Product in the United Kingdom and Republic of Ireland in a separate internal account (the "UK and Ireland Sales Account").

10.4 Shire shall within thirty days of the end of each Quarter deduct from the UK and Ireland Sales Account, Shire's, Janssen's and their respective Affiliates Direct Expenses incurred in selling the Licensed Product in the United Kingdom and Republic of Ireland during the previous Quarter.

10.5 Shire shall pay to Janssen the sum deducted under Clause 10.4 above in respect of Janssen's Direct Expenses within 30 days of receiving an appropriate invoice from Janssen in respect of such Direct Expenses. Shire shall be entitled to retain the sum deducted under Clause 10.4 above in respect of Shire's Direct Expenses.

10.6 Shire shall pay to Janssen one half of the sums remaining in the UK and Ireland Sales Account after deduction of the Direct Expenses and Shire shall be entitled to transfer the remaining sums held in the UK and Ireland Sales Account to Shire's own account.

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10.7 In this Clause 10 the term "Direct Expenses" shall mean all direct expenses incurred by Shire, Janssen and their respective Affiliates in selling the Licensed Product in the United Kingdom and Republic of Ireland including without limitation the cost of promotional campaigns, the cost of visits to Doctors and hospitals, distribution and warehousing costs, the cost of the Licensed Product itself, and regulatory costs. Shire shall be entitled to include in its Direct Expenses a reasonable fee calculated as a percentage of the Net Sales Value of the Licensed Product to cover Shires direct financing and administration costs.

10.8 All business decisions relating to the sale and promotion of the Licensed Product in the United Kingdom and the Republic of Ireland shall be at Shire's sole discretion including without limitation the decision as to when to launch the Licensed Product provided that if the United Kingdom or the Republic of Ireland is used as the Rapporteur Country for EC Product Approval then subject to Clause 4.5 Janssen shall be responsible for the business decisions relating to that application for Product Approval.

10.9 Shire shall prepare a proposed plan for the marketing and sale of the Licensed Products in the United Kingdom and the Republic of Ireland and shall submit its proposed plan to Janssen not less than 120 days prior to the then forecast date for the first Commercial Delivery in the United Kingdom or the Republic of Ireland. The parties shall meet promptly after submission of the proposed plan to agree a final marketing plan for the United Kingdom and the Republic of Ireland.

10.10 In this Clause 10 the term "Licensed Product" shall mean any product containing Galanthamine which is used for or intended to be used for the treatment of Alzheimer's disease and related dementias in the United Kingdom and/or the Republic of Ireland.

11. Trade Marks

11.1 Janssen shall select the trade mark that it wishes to be used in relation to the Licensed Product throughout the Territory and shall notify Shire of its selection to Shire as soon as possible and in any event at least by the date of filing of the first application for Product Approval.

11.2 In countries where there are reasonable grounds for not using the trade mark selected pursuant to Clause 11.1 above Janssen may select a different trade mark to use in such country in relation to the Licensed Product and shall notify its selection to Shire.

11.3 Shire shall use reasonable endeavours to register in its own name and maintain the Trade Mark selected by Janssen pursuant to Clause 11.1 in the United Kingdom and the Republic of Ireland (unless there are reasonable grounds for not using the same Trade Mark in the United Kingdom and/or the Republic of Ireland) and the costs of registering and maintaining such Trade Mark registrations shall be paid by Shire but shall be considered as a Direct Expense for the purposes of Clause 10.4.

11.4 Janssen shall use reasonable efforts consistent with its normal business practices to register in its own name and maintain the Trade Marks in the Major Countries and the costs of registering and maintaining such Trade Mark registrations shall be paid and borne by Janssen.

11.5 All goodwill arising out of use of the Trade Marks by Janssen and its Affiliates in the United Kingdom and the Republic of Ireland shall belong to Shire and Janssen shall from time to time as and when requested by Shire promptly execute confirmatory assignments confirming that such goodwill vests in Shire.

11.6 Janssen shall in respect of the Territory and Shire shall in respect of the United Kingdom and the Republic of Ireland use reasonable endeavours consistent with their normal business practices to maintain, protect and enforce the Trade Marks using counsel of their own choice.

12. Patents

12.1 Infringement of the Patents

12.1.1 Janssen shall promptly notify Shire with such details as Janssen has in its possession of all infringements of the Patents of which Janssen and/or its Affiliates and/or Business Partners become aware.

12.1.2 Janssen shall keep Shire regularly informed of the progress of and developments in, any proceedings against infringers of the Patents including any settlement discussions with such infringers.

12.1.3 Janssen may negotiate a settlement with an infringer of the Patents but shall not conclude any such settlement without Shire's prior written approval of the terms of the settlement, such approval not be unreasonably withheld or delayed.

12.1.4 If both of the following conditions are met:

12.1.4.1 Janssen after having commenced proceedings against an infringer of the Patents fails to stop the infringing activities within 180 days of the date on which the infringement was notified to Janssen; and

12.1.4.2 products which infringe the Patents take more than 20% by value of sales of the Licensed Product for two consecutive Quarters in the country in which the infringement occurs;

then in respect of such country only the Secondary Royalty Rate shall apply for as long as products infringing the Patents take more than 20% by value of sales of the Licensed Product in such country.

12.1.5 Any damages, costs, awards or other sums received by Janssen arising out of any proceedings brought by Janssen for infringement of the Patents (or the settlement of any such proceedings) shall be divided in accordance with the relevant provisions of the Synaptech-Janssen Licence Agreement (in the case of infringements within the Janssen Territory) and the Shire-Janssen Sub-licence Agreement (in the case of infringements within the Shire Territory). Janssen shall pay to Shire the Secondary Royalty Rate on any such sums retained by Janssen after the aforementioned division as if such retention formed part of the Net Sales Value.

12.2 Infringement of the Manufacturing Patents

12.2.1 Shire and Janssen shall notify each other forthwith in writing of any infringement or suspected or threatened infringement of the Manufacturing Patents which shall at any time come to their knowledge. Such notice shall include any information concerning the infringement which is known to the party giving notice at the date of the notice.

12.2.2 Janssen may at its sole discretion and at its own expense take proceedings against infringers of the Manufacturing Patents in which case Shire shall provide such assistance as Janssen may reasonably request in connection with such proceedings including without limitation:-

12.2.2.1 making available to Janssen such records information and evidence in its possession or control which may be of assistance to Janssen;

12.2.2.2 giving Janssen authority to file and prosecute such proceedings; and

12.2.2.3 giving Shire's consent to be named as a party in any such proceedings provided that Janssen indemnifies Shire against any award of costs or damages made against Shire (by the court, tribunal or other body before which the proceedings have been brought) as a consequence of being named in such proceedings.

12.2.3 Janssen shall keep Shire fully informed of the progress of and developments in any such proceedings including any settlement discussions with such infringers.

12.2.4 Janssen may negotiate settlement with an infringer of the Manufacturing Patents but shall not conclude any such settlement without Shire's prior written approval of the terms of the settlement such approval not to be unreasonably withheld or delayed.

12.2.5 If for any reason Janssen fails to take proceedings against any infringer of the Manufacturing Patents within 90 days of being notified of such infringement then Shire may at its sole discretion and at its own cost and expense take proceedings against such infringer in which case Janssen shall provide such assistance as Shire may reasonably request in connection with such proceedings including without limitation making available to Shire such records information and evidence in its possession or control which may be of assistance to Shire.

12.2.6 Janssen shall be entitled to retain up to 50% of each Quarter's royalties otherwise payable to Shire under Clause 6.1 in respect of the country of the Territory where infringement proceedings have been commenced by Janssen under the Manufacturing Patents, to cover up to a maximum of 50% of the reasonable out of pocket expenses incurred by Janssen or its designated Affiliate in bringing such infringement proceedings.

12.2.7 Any damages, costs, awards or other sums received by Janssen arising out of the proceedings brought by Janssen for infringement of the Manufacturing Patents (or the settlement of any such proceedings) shall be divided between the parties in the following order of priority:

12.2.7.1 Janssen shall be entitled to its reasonable out of pocket expenses actually incurred by Janssen or its designated Affiliate in respect of the proceedings insofar as such expenses have not already been deducted from the royalties payable to Shire pursuant to Clause 12.2.6;

12.2.7.2 Shire shall be entitled to a sum equal to any royalties withheld pursuant to Clause 12.2.6; and

12.2.7.3 Janssen shall be entitled to retain the remainder.

12.3 Infringement of Third Party Rights

12.3.1 If the manufacture of Galanthamine using the Manufacturing Intellectual Property Rights constitutes an infringement of the rights of a third party in a country of the Janssen Territory, each party shall, as soon as it becomes aware of such infringement, notify the other party thereof in writing giving in the same notice full details known to it of the rights of such third party and the extent of any potential infringement.

12.3.2 The parties shall after receipt of such notice referred to in Clause 12.3.1 above discuss the situation and to the extent necessary attempt to agree a course of action in order to permit Janssen to practice the licences granted under this Agreement. Such course of action may include (1) obtaining an appropriate licence from such third party; or (2) contesting any claim or proceedings bought by the third party.

12.3.3 If within 21 days the parties fail to agree upon an appropriate course of action the party being sued may decide upon the course of action in the interest of further development and/or commercialisation of the Licensed Product.

12.3.4 The party being sued shall have the right to negotiate an appropriate licence from such third party and shall keep the other party fully informed as to progress of such negotiations. The party negotiating such licence shall use its reasonable efforts to minimise the amount of licence fees and royalties payable in respect of any such licence.

12.3.5 50% of any licence fees or royalties paid by Janssen under any licence negotiated pursuant to Clause 12.3.4 above shall be creditable against royalties due to Shire under this Agreement in respect of the countries covered by such third party rights only provided that in no event shall the royalties payable under Clause 6.1 be reduced under the provisions of this Clause 12.3.5 by more than 50%.

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12.3.6 If Janssen decides to defend a suit or claim referred to in Clause 12.3.1 above then Janssen shall have the right to apply up to 50% of each Quarter's royalties otherwise payable to Shire under Clause 6.1 in respect of countries covered by such third party rights on sales of the allegedly infringing Licensed Products against its reasonable legal and experts' fees in defending such suit or claim.

12.3.7 Clauses 12.3.5 and 12.3.6 shall only apply in respect of claims that the use of the Manufacturing Intellectual Property Rights for the manufacture of Synthetic Galanthamine infringes the rights of a third party and shall not apply to any allegation or claim relating to the use and/or formulation of the Licensed Product and/or delivery methods for the Licensed Product.

13. Product Liability & Breach Of Warranty By Synaptech

13.1 Product Liability

13.1.1 Janssen shall assume all risks associated with the importation, manufacture, use, keeping, offer for sale or supply sale or supply by through or on behalf of Janssen, its Affiliates and Business Partners of Licensed Products (and related materials) in the Territory including without limitation all claims based upon product liability laws.

13.1.2 Without limit of time Janssen shall defend, indemnify and hold harmless Shire, its Affiliates, its directors, officers, employees and consultants and those of its Affiliates from and against any and all claims, demands, losses, damages and/or expenses (including without limitation reasonable legal and experts' fees) arising from or in connection with any manufacture, use, sale or supply by Janssen, its Affiliates and/or Business Partners of Galanthamine and/or Licensed Product in the Territory except to the extent that any such claims, demands, losses, damages and/or expenses result directly from the gross negligence of Shire.

13.1.3 Without limit of time, Shire shall defend indemnify and hold harmless Janssen, its Affiliates, its directors, officers, employees and consultants and those if its Affiliates from and against any and all claims, demands, losses, damages and/or expenses (including without limitation reasonable legal and experts' fees) arising from or in connection with any manufacture use, sale or supply by Shire and/or its Affiliates of Galanthamine and/or Licensed Product in the Excluded Territory except to the extent that any such claims, demands, losses, damages and/or expenses result directly from the gross negligence of Janssen, its Affiliates and/or Business Partners.

13.1.4 Without limit of time, Shire shall indemnify and hold harmless Janssen, its Affiliates, its directors, officers, employees and consultants and those of its Affiliates from and against any and all losses, damages and/or expenses (including without limitation reasonable legal and experts fees) incurred by the aforementioned as a result of third party claims arising directly and solely from the negligence of Shire in arranging supplies of Natural Galanthamine for Janssen pursuant to Clause 16.1.

13.2 Breach of Warranty by Synaptech

13.2.1 If Synaptech is in breach of any of the warranties set out in the Synaptech-Shire Licence Agreement and/or those set out in the Synaptech-Janssen Licence Agreement then Shire and Janssen shall discuss the breach and if appropriate Shire and/or Janssen shall take proceedings against Synaptech in respect of such breach.

13.2.2 Any sums received by Shire and/or Janssen in respect of Synaptech's breach of the warranties set out in the Synaptech-Shire Licence Agreement and/or the Synaptech-Janssen Licence Agreement shall (after deduction of any reasonable out of pocket expenses incurred by Shire and/or Janssen in taking action against Synaptech) be divided between the parties on a fair and reasonable basis taking into account the respective losses suffered by the parties as a consequence of such breach of warranty. If the parties are unable to agree on the division then either party may refer the matter to an arbitration pursuant to Clause 28.12.

13.2.3 Except as set out in Clause 13.2.2, Shire shall not be liable to Janssen in respect of any breach of the warranties set out in Clause 14 of the Shire-Janssen Sub-licence Agreement.

14. **Development Data, International Registration File and Improvements**

14.1 Development Data

14.1.1 All Development Data and other documentation arising out of or in connection with development of the Licensed Products or other information concerning the Licensed Products shall be exchanged between the parties as and when it becomes available or upon demand by either party.

14.1.2 The Development Data shall be jointly owned by Janssen and Shire. Janssen shall have the exclusive right to use the Development Data in the Territory and Shire shall have the exclusive right to use the Development Data in the Excluded Territory.

14.1.3 If requested by Synaptech pursuant to Clause 10.1 of the Synaptech-Janssen Licence Agreement and/or Clause 10.1 of the Synaptech-Shire Licence Agreement Janssen and Shire shall jointly license the use of the Development Data in connection with Alzheimer's disease and related dementias in Japan. Janssen and Shire shall divide any sums they receive in respect of such licence on a fair and reasonable basis taking into account, without limitation, factors such as the relative investments made by the parties in the development of the Licensed Products both before and after the date of this Agreement and the parties relative share of the risk in the development of the Licensed Products. If they are unable to agree the division then either party may refer the matter to arbitration pursuant to Clause 28.12.

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14.1.4 Shire shall have the exclusive right to use the Development Data in Japan in connection with CFS and other indications. Shire may disclose the Development Data to a licensee for use in Japan provided that such licensee is subject to confidentiality obligations equivalent to those set out in Clause 15.

14.2 International Registration File

14.2.1 Janssen shall compile and own the International Registration File, subject to the parties joint ownership of all the Development Data upon which the International Registration File is based.

14.2.2 When Janssen has compiled the International Registration File, Janssen shall, at the request of Shire, promptly provide Shire with a full and complete copy.

14.2.3 Shire and its Affiliates shall be entitled to submit the International Registration File to the regulatory authorities in the Excluded Territory for the purpose of obtaining Product Approvals provided that if the United Kingdom or the Republic of Ireland is used as the Rapporteur Country for EC Product Approval then subject to Clause 4.5 Janssen shall be responsible for the business decisions relating to that application for Product Approval.

14.3 Improvements

14.3.1 The parties shall disclose in writing to each other free of charge all Improvements developed or acquired by the parties.

14.3.2 Janssen shall have a non-exclusive, royalty-free licence to use Improvements developed or acquired by Shire and/or its Affiliates in the Territory in accordance with the provisions of this Agreement, together with the right to grant sub-licences thereunder.

14.3.3 Shire shall have a non-exclusive, royalty-free licence to use Improvements developed or acquired by Janssen and/or its Affiliates in the Excluded Territory in accordance with the provisions of this Agreement, together with the right to grant sub-licences thereunder.

14.3.4 The parties shall disclose in writing to each other free of charge all Manufacturing Improvements developed or acquired by the parties.

14.3.5 Janssen shall have a non-exclusive royalty-free licence to use Manufacturing Improvements developed or acquired by Shire and/or its Affiliates in the Territory and the United Kingdom and the Republic of Ireland in accordance with the provisions of this Agreement, together with the right to grant sub-licences thereunder.

14.3.6 Shire shall have a non-exclusive, royalty-free, worldwide licence to use Manufacturing Improvements developed or acquired by Janssen and/or its Affiliates in accordance with the provisions of this Agreement together with the right to grant sub-licences thereunder.

15. Confidentiality

15.1 Shire and Janssen undertake to each other to keep, and shall procure that their respective Affiliates, or Business Partners, employees, directors, officers, consultants and contractors (including those of any Affiliate or Business Partner) shall keep, confidential all information supplied to each other during or in anticipation of this Agreement (including without limitation the Development Data) however obtained and in whatever form (the "Confidential Information") provided that Confidential Information shall not include the following:-

15.1.1 information which at the time of disclosure by one party to the other is in the public domain;

15.1.2 information which after disclosure by one party to the other becomes part of the public domain by publication except by breach of this Agreement;

15.1.3 information which the receiving party can establish by competent proof was already in its possession at the time of its receipt and was not acquired directly or indirectly from the other party; and

15.1.4 information received from third parties who were lawfully entitled to disclose such information.

15.2 Any Confidential Information received from the other party shall not be used for any purpose other than as provided or anticipated under this Agreement.

15.3 The confidentiality and non-use obligations contained in this Agreement shall continue for the duration of this Agreement and for a period of 10 years after termination or expiry of this Agreement.

15.4 The provisions of this Clause 15 shall in no event prevent Janssen and/or Shire from disclosing any Development Data to regulatory authorities or other governmental agencies in support of any application for regulatory approvals or any amendments thereof in accordance with the provisions of this Agreement or in general whenever requested to disclose such information under any applicable law or regulation provided that the party intending to disclose any Development Data shall notify the other party of its intention and the identity of the intended recipient at least 7 days prior to the date of disclosure.

15.5 The provisions of this Clause 15 shall not prevent the parties from complying with any contractual obligations they may have to Synaptech, the third party holder of patent rights covering the use of Galanthamine for the treatment of CFS and/or Chiroscience provided that such third parties are or will be bound by confidentiality obligations similar to those set out in this Clause 15.

16. Manufacture And Supply

Based upon the Co-Development Plan as at the date of this Agreement, the parties envisage that it will be necessary to plan the supply of plant bulbs and Natural Galanthamine for an initial period of approximately 2 years following first Commercial Delivery. It is thought that about 1000kg of Natural Galanthamine will be required in the first year following first Commercial Delivery and 2000kg in the second year, thereafter the parties may switch to Licensed Product manufactured from Synthetic Galanthamine. Within 6 months of the date of this Agreement Shire and Janssen shall enter into a supply agreement in respect of Galanthamine Raw Material (and if feasible at the time, Finished Product) which shall include without limitation provisions equivalent to those set out below:-

16.1 Supply of Natural Galanthamine

16.1.1 Shire shall be responsible for arranging supplies of Natural Galanthamine but shall consult with Janssen as and when necessary. Janssen shall notify Shire with its final reasonable requirements for Natural Galanthamine in time for Shire to make the appropriate arrangements. Shire shall place orders for plant bulbs and extraction services (based upon such final reasonable requirements as notified to Shire) on behalf of Janssen and in doing so shall act as Janssen's agent in this regard. Shire shall use reasonable skill and care to manage and plan on behalf of Janssen the supply of plant bulbs and extraction so as to meet Janssen's reasonable requirements as notified to Shire in accordance with a detailed forecast mechanism to be included in the supply agreement. Where Janssen wishes to change its requirements, Shire shall use its reasonable endeavours to implement such changes but shall not be liable if it is not technically and/or contractually feasible to do so. Janssen acknowledges that with existing technology and propagation lead times it may not be possible to produce quantities of Natural Galanthamine in excess of those set out in Clause 16.1.6. Shire shall only be liable to Janssen for any failure to fulfil Janssen's reasonable requirements for Natural Galanthamine if:-

16.1.1.1 the cause of such failure is Shire's failure to use reasonable skill and care to manage and plan supplies of Natural Galanthamine to meet Janssen's reasonable requirements; and

16.1.1.2 the cause of such failure was within the reasonable control of Shire; and

16.1.1.3 Janssen's total reasonable requirements notified to Shire are within the quantity limitations stated in Clause 16.1.6

16.1.2 Janssen and Shire shall divide harvested plant bulb material resulting from a years harvest according to the proportions in which they paid for the original plant bulb material that produced that year's harvest. For example, if for one year Janssen paid 97.5% of the cost of planting bulbs and Shire paid 2.5% then 97.5% of the quantity of harvested plant bulb material resulting from that year will be owned by Janssen and 2.5% by Shire.

16.1.3 Janssen and Shire shall divide the Natural Galanthamine resulting from the extraction from plant bulb material according to the proportions in which they own the plant bulb material as set out in Clause 16.1.2 above. For example if Shire owns 2.5% and Janssen owns 97.5% of the plant bulb material sent for extraction then Shire shall own 2.5% and Janssen shall own 97.5% of the resulting Natural Galanthamine.

16.1.4 If at any time one party shall have Natural Galanthamine in excess of its requirements and the other party shall have a shortfall in its requirements then the excess may be transferred to make up all or part of the shortfall and the transfer price shall be as set out in Clause 16.1.5 below.

16.1.5 The costs of Natural Galanthamine supplied to Janssen under this Clause 16.1 shall be Shire's external costs of producing the supply plus a 5% fee to cover Shire's administration and overhead costs. For the avoidance of doubt any licence fees, development fees or royalties payable to third parties shall form part of the external costs. This Clause 16.1.5 shall apply only in respect of supplies of Natural Galanthamine (1) for use in trials referred to in the Co-development Plan or (2) upon which royalties are to be paid pursuant to Clauses 6.1 of this Agreement.

16.1.6 Janssen shall not be required to contribute to the purchase cost of any capital equipment that is required as part of the extraction process provided that Janssen's orders for Natural Galanthamine do not exceed 1,000 kilograms during the first 12 months following the first Commercial Delivery, 2000 kilograms during the second 12 months and none thereafter.

16.1.7 Shire shall retain ownership of any intellectual property rights relating to the extraction process used.

16.2 Transition to Synthetic Galanthamine

16.2.1 Janssen shall decide for the Territory, when (if at all) to make the transition from using Natural Galanthamine in the Licensed Product to using Synthetic Galanthamine. However Janssen shall consult fully with Shire on the timetable for the transition and use reasonable endeavours to ensure that a smooth transition is effected.

16.2.2 Shire shall decide for the Excluded Territory when (if at all) to make the transition from using Natural Galanthamine in the Licensed Product to using Synthetic Galanthamine. However Shire shall consult fully with Janssen on the timetable for the transition and use reasonable endeavours to ensure that a smooth transition is effected.

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16.3 Supply of Synthetic Galanthamine

16.3.1 If Janssen or any of its Affiliates develop or acquire the capacity to manufacture Galanthamine Raw Material then Janssen (or its Affiliates as the case may be) shall at the request of Shire supply Shire's requirements for Galanthamine Raw Material and/or Finished Product in accordance with a detailed forecast mechanism to be included in the supply agreement. Janssen shall also at the request of Shire supply Shire (or any third party designated by Shire) with the requirements for Galanthamine Raw Material and/or Finished Product of any Synaptech licensee outside the Territory provided that the Synaptech licensee's requirements, are for Galanthamine Raw Material and/or Finished Product which is identical to that manufactured by Janssen or its Affiliates for use within the Territory. Any such supply for sale in respect of Synaptech's licensee's requirements will be upon reasonable arms length terms to be agreed with Janssen and for the avoidance of doubt the provisions of Clause 16.3.2 shall not apply in respect of such sale.

16.3.2 The price at which Janssen supplies Galanthamine Raw Material and/or Finished Product to Shire shall be Janssen's Standard Cost of Galanthamine plus a 5% fee on such cost to cover administration and overheads.

16.3.3 For the avoidance of doubt nothing in this Agreement shall require:

16.3.3.1 Shire to purchase Galanthamine Raw Material and/or Finished Product from Janssen; or

16.3.3.2 Janssen to purchase Galanthamine Raw Material and/or Finished Product from Shire.

16.4 Renegotiation of the Chiroscience Agreement

16.4.1 Shire and Janssen shall promptly commence negotiations with Chiroscience and shall use their reasonable endeavours to negotiate the following changes and additions to the Chiroscience Agreement:-

16.4.1.1 Shire to have the right to grant Janssen the licences set out in Clauses 2.1.1.2 and 2.1.1.3.

16.4.1.2 The early and full scale-up of production of Synthetic Galanthamine to be carried out by Janssen.

16.4.1.3 The licence fees payable to Chiroscience in respect of production of Synthetic Galanthamine to be reduced as a consequence of Chiroscience doing less of the development work than was originally envisaged.

16.4.1.4 Simplify the provisions of the Chiroscience Agreement insofar as practical.

16.4.2 Janssen acknowledges that Chiroscience may not agree to all or any of the above changes or additions described in Clause 16.4.1 above. In such event Janssen and Shire shall promptly meet to discuss a further course of action to enable Janssen to obtain supplies of Galanthamine Raw Material under such conditions that the Licensed Product can be marketed by Janssen under similar economic and commercial conditions as currently contemplated and specified in the rest of this Agreement. Provided that nothing in this Clause 16.4 shall require Shire to change any of the provisions of this Agreement.

17. **Chronic Fatigue Syndrome**

17.1 Shire and its Affiliates may at their sole discretion develop Galanthamine for use in the treatment of CFS and Janssen acknowledges Shire's right to do so under Shire's licence agreement with the holder of the patents claiming the use of Galanthamine for the treatment of CFS and that such licence agreement requires Shire to use its reasonable endeavours to develop and extend the market for Galanthamine as a treatment for CFS. Shire shall only market and supply Galanthamine for the treatment of CFS within the Territory and the United Kingdom and the Republic of Ireland in association with Janssen (to the exclusion of all others) and in accordance with the provisions set out in this Clause 17.

17.2 Shire shall from time to time consult with Janssen concerning the conduct and objectives of studies to be carried out in relation to the use of Galanthamine for the treatment of CFS.

17.3 If both of the following conditions are met then Janssen shall join Shire in the development of Galanthamine for the treatment of CFS and Janssen shall promote market and sell Galanthamine for the treatment of CFS on and subject to the terms set out in Clause 17.5 :-

17.3.1 Shire's phase II study or its phase III study in relation to CFS is successful according to the success criteria to be agreed by the parties within 90 days of the date of this Agreement; and

17.3.2 there is a reasonable prospect that regulatory approval can be obtained in the majority of the Major Countries to sell Galanthamine for the treatment of CFS.

17.4 If the parties fail to agree as to whether or not the conditions set out in Clauses 17.3.1 and 17.3.2 have been met or the success criteria referred to in Clause 17.3.1 have not been agreed within the said 90 day period then either party may refer the matter to an expert for resolution in accordance with Clause 28.13;

17.5 Subject to the conditions set out in Clause 17.3 being met, Janssen shall join Shire in the development of Galanthamine for the treatment of CFS and Janssen shall promote market and sell Galanthamine for the treatment of CFS on and subject to the following terms:-

17.5.1 Janssen shall pay to Shire a milestone payment of £1,000,000 (sterling) within thirty days of the conditions set out in Clause 17.3 being met.

17.5.2 Janssen shall pay to Shire either:-

17.5.2.1 one and one half times the cost incurred by Shire in developing Galanthamine for the treatment of CFS within thirty days of Shire's phase II study referred to in Clause 17.3.1 meeting the success criteria referred to in Clause 17.3.1 (payment shall be made within 30 days); or

17.5.2.2 two and a quarter times the cost incurred by Shire in developing Galanthamine for the treatment of CFS within thirty days of Shire's phase III study referred to in Clause 17.3.1 meeting the success criteria referred to in Clause 17.3.1 (payment shall be made within 30 days).

17.5.3 The cost of further development of Galanthamine for the treatment of CFS shall be shared between Janssen and Shire on the same basis as for the development of the Licensed Product with the total development cost attributed to each country being apportioned according to IMS data on the size of the total market for all pharmaceutical products in that country and Janssen bearing 100% of the apportioned development costs in countries where it has an exclusive licence and Janssen and Shire dividing the apportioned development costs equally in countries where Shire and Janssen co-promote the resulting products.

17.5.4 Shire shall grant to Janssen an exclusive sub-licence to develop, use, keep, sell and/or dispose of Galanthamine for the treatment of CFS throughout the Territory.

17.5.5 The other terms shall, unless the parties agree otherwise, be the same as those set out in this Agreement and the Shire-Janssen Sub-licence Agreement including without limitation the terms relating to royalty rates and buy-back options.

18. Other Indications

18.1 Janssen acknowledges that Shire has rights to use Galanthamine for the treatment of indications other than Alzheimer's disease and CFS such as the treatment of mania and improvements in benzodiazepine treatment.

18.2 Shire may at its sole discretion develop Galanthamine for use in the treatment of indications other than Alzheimer's disease and CFS including without limitation the treatment of mania and improvements in benzodiazepine treatment and Janssen acknowledges Shire's right to do so provided that, subject to Clause 18.4, to preserve the exclusive rights granted to Janssen under this Agreement and the Shire-Janssen Sub-licence Agreement Shire shall only market and supply Galanthamine for the treatment of such indications in the Territory and the United Kingdom and the Republic of Ireland in association with Janssen to the exclusion of all others) and in accordance with the provisions of this Agreement. Shire acknowledges that Janssen has no obligation to co-develop and/or market Galanthamine for the treatment of such other indications under the provisions of this Agreement except when conditions equivalent to those set out in Clause 17.3 are met.

18.3 Subject to Clause 18.4, provisions equivalent to those set out in Clause 17 shall apply in respect of the use of Galanthamine for the treatment of mania and improvements in benzodiazepine treatment provided that, Janssen shall not be required to make additional milestone payments.

18.4 Shire shall be entitled to develop, market and supply Galanthamine for use in association with benzodiazepine or for the treatment of other indications either by itself or in association with third parties provided that Shire can clearly demonstrate that the marketing, promotion and sales of Galanthamine for such purpose will not adversely affect Janssen's marketing, promotion and sales of the Licensed Product. For the avoidance of doubt Shire shall not market or sell Galathamine for such indications without the prior approval of Janssen such approval not to be unreasonably withheld or delayed. Janssen may withhold such approval if the exclusive rights granted under this Agreement and the Shire-Janssen Sub-licence Agreement would be prejudiced by Shire's marketing and supply of Galanthamine for such indications. If and only if Janssen gives its approval pursuant to this Clause 18.4 then Shire shall be entitled to use the Development Data free of charge in relation to such approved indications worldwide subject to reasonable non-financial conditions relating to the use of the Development Data.

19. Buy Back Options

19.1 Janssen hereby grants to Shire an option for a period of 6 months after the fifth anniversary of the first Commercial Delivery in the country concerned to acquire the exclusive rights to market and sell the Licensed Product in any one of France, Germany, Italy or Spain in consideration for the payment by Shire to Janssen of a sum equivalent to 3½ times the average annual value of the Net Sales Value of the Licensed Product sold in the country selected by Shire calculated over the 9th, 10th, 11th, 12th, 17th, 18th, 19th and 20th Quarters following the date of first Commercial delivery in such country.

19.2 Janssen hereby grants to Shire an option for a period of 6 months after the tenth anniversary of the first Commercial Delivery in the country concerned to acquire the exclusive rights to market and sell the Licensed Product in any one of France, Germany, Italy or Spain in consideration for the payment by Shire to Janssen of a sum equivalent to 2½ times the average annual value of the Net Sales Value of the Licensed Product sold in the country selected by Shire over the previous 4 Quarters.

19.3 Shire shall exercise the options set out in Clauses 19.1 and 19.2 by notifying Janssen with the name of the country selected by Shire. Upon receipt of written notice by Shire exercising its option the parties shall execute the necessary documentation to effect the grant back of the exclusive rights by Janssen together with the transfer of the Product Licence and any registrations for Trade Marks in the country selected subject to the payment by Shire of the purchase price, as stated in Clause 19.1 or 19.2 as appropriate. The parties shall use reasonable endeavours to ensure that a smooth transfer of the rights to market the Licensed Product takes place in the country concerned.

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20. Other Cholinesterase Inhibitors

20.1 If during the term of this Agreement Janssen or any of its Affiliates or Business Partners (subject to Clause 20.5) shall launch a cholinesterase inhibitor (other than the Licensed Product) for use in the treatment of Alzheimer's disease, CFS or any other indication which Janssen and Shire have or are in the process of developing (a "competing product") then Shire may at its option make the following election with respect to each Major Country and the countries of the Territory which are not Major Countries (which, for the purpose of this Clause 20, shall be treated as a single block, the "Non-Major Countries") either:-

20.1.1 elect to receive from Janssen minimum royalties from the date of launch of the competing product in respect of sales of the Licensed Product in the countries of the Territory concerned. The minimum royalties shall be calculated by forecasting the next three years Net Sales Value of the Licensed Product solely on the basis of the trend evident from the preceding 3 years' Net Sales Value. For the avoidance of doubt when making such forecast no account shall be taken of impact of the launch of the competing product. The minimum royalties for the three year period shall be calculated on 80% of the forecast Net Sales Value for such 3 year period. At the end of subsequent 3 year periods the minimum royalties for the following 3 year period shall be recalculated on the same basis and Shire shall at its option determine whether or not to accept minimum royalties for a further 3 year period; ~~or~~

20.1.2 elect to repurchase from Janssen the exclusive rights to market and sell the Licensed Product in the countries of the Territory concerned in consideration of the relevant payment as stated below:-

Remaining Life of Patent	Purchase Price as a Multiple of Net Sales Value (1)
3 years or longer	1.5 times Net Sales Value
Less than 3 years	0.8 times Net Sales Value
Patent not in force	0.5 times Net Sales Value

(1) Based upon the audited figures for the four completed preceding Quarters

This option to repurchase the exclusive rights from Janssen shall expire 6 years after the date upon which the last of the Patents ceases to be in force.

20.2 If Shire decides to exercise its option under Clause 20.1.2 to repurchase from Janssen the exclusive rights to market and sell the Licensed Product in any country within the Janssen Territory and Shire procures Synaptech's consent to such repurchase then Janssen shall agree with Synaptech that Janssen's rights and licences under the Synaptech-Janssen Licence Agreement shall terminate in respect of such countries.

20.3 If Shire elects to receive minimum royalties pursuant to Clause 20.1.1 in respect of any Major Country and/or the Non-Major Countries, then the royalties payable under the Shire-Janssen Sub-licence Agreement in respect of the same countries shall be subject to minimum royalties calculated in accordance with the principles set out in Clause 20.1.1.

20.4 If Shire elects to exercise its option under Clause 20.1.2 in respect of any country within the Territory then Janssen shall at the same time as payment of the relevant purchase price execute all necessary documentation to effect the repurchase of the exclusive rights by Shire and to transfer to Shire (or its designated transferee) any Product Licences and registrations for Trade Marks in such country. The parties shall use reasonable endeavours to ensure that a smooth transfer of the rights to market the Licensed Product takes place in such country.

20.5 Clause 20.1 shall not apply to sales of competing products made by Janssen's Business Partners provided that such competing products have not been developed, acquired and/or licensed by Janssen or its Affiliates.

21. Licence Agreements

21.1 Janssen shall use reasonable endeavours consistent with its normal business practices to :-

21.1.1 comply with its obligations under the Synaptech-Janssen Licence Agreement; and

21.1.2 avoid any act or omission within Janssen's reasonable control which may cause the Synaptech-Janssen Licence Agreement to terminate in whole or in part other than by exercising any right of termination Janssen may have under the Synaptech-Janssen Licence Agreement.

21.2 Any dispute as to whether Janssen has failed to comply with its obligations to use reasonable endeavours under the Synaptech-Janssen Licence Agreement shall be resolved in accordance with Clause 19.11 of the Synaptech-Janssen Licence Agreement and as regards compliance with Clause 21.1 of this Agreement, such decision shall be binding upon Shire and without prejudice to Janssen's discretionary right to exercise its rights of termination under the Synaptech-Janssen Licence Agreement.

21.3 Janssen shall not exercise any right to terminate the licences granted under the Synaptech-Janssen Licence Agreement without first consulting Shire.

21.4 Shire shall use reasonable endeavours consistent with its normal business practices to

21.4.1 comply with its obligations under the Synaptech-Shire Licence Agreement; and

21.4.2 avoid any act or omission within its reasonable control which may cause the Synaptech-Shire Licence Agreement to terminate in whole or in part other than by exercising any right of termination Shire may have under the Synaptech-Shire Licence Agreement.

21.5 Shire shall not exercise any right to terminate the licences granted under the Synaptech-Shire Licence Agreement without obtaining Janssen's prior approval.

21.6 In the event of any conflict between the provisions of the Shire-Janssen Sub-licence Agreement and the provisions of this Agreement, the provisions of this Agreement shall prevail to the extent of the conflict.

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22. Duration

This Agreement and the licences granted under Clause 2 shall come into force on the date of this Agreement and unless terminated earlier in accordance with the provisions of this Agreement, this Agreement shall expire upon cessation of all obligations to pay royalties under Clause 6 and thereafter Janssen shall have a fully paid up royalty free licence in respect of the Licensed Products.

23. Termination

23.1 Termination by Either Party

This Agreement and the licences granted in Clause 2 may be terminated by a party to this Agreement:-

23.1.1 Material Breach

23.1.1.1 Forthwith by notice in writing given at any time if the other party is in material breach of any of its obligations hereunder and in the case of a material breach capable of remedy within 45 days, the material breach has not been remedied within 45 days of the defaulting party receiving notice specifying the material breach and requiring its remedy.

23.1.1.2 A material breach of this Agreement is (1) a wilful act or omission by the party in breach that would deprive the other party of a major part of the value of what it had contracted for and for which damages are not an adequate remedy; or (2) a persistent breach of the provisions of this Agreement. Any dispute as to whether or not a material breach of this Agreement has been committed shall be referred to an arbitrator for resolution pursuant to Clause 28.12.

23.1.2 Insolvency

Forthwith by notice in writing given at any time if an order is made or a resolution is passed for the winding up of the other party (other than voluntarily for the purposes of solvent amalgamation or reconstruction) or an order is made for the appointment of an administrator to manage the other party's affairs, business and property or if a receiver (which expression shall include an administrative receiver) is appointed of any of the other party's assets or undertaking or if circumstances arise which entitle the court or a creditor to appoint a receiver or manager or which entitle the court to make a winding-up order or if a voluntary arrangement is proposed in respect of the other party or if the other party takes or suffers any similar or analogous action in consequence of debt.

23.2 Termination by Shire

This Agreement and the licences granted in Clause 2 may be terminated by Shire forthwith by notice in writing to Janssen given at any time if:-

23.2.1 Non-Payment

Janssen fails to pay any royalties or other initial or milestone payments due under this Agreement (including those due under Clauses 3.1, 3.2 and 6.1) within 45 days of receiving notice from Shire demanding such payment;

23.2.2 Challenge to the Manufacturing Patents

Janssen or its Affiliates or Business Partners dispute or directly or indirectly assists any third party to dispute the validity or enforceability of the Manufacturing Patents or any of the claims thereof;

23.2.3 Unjustifiable Delay To The Co-Development Plan

Shire notifies Janssen pursuant to Clause 9.2.3 to take immediate action to rectify its efforts so as to comply with the timetable set out in the Co-Development Plan and Janssen has not within 3 months of the date of such notice used reasonable efforts to comply with the said timetable. Any dispute as to whether or not Janssen has used reasonable efforts to comply with the said timetable shall be referred to arbitration pursuant to Clause 28.12; or

23.2.4 Termination of Licences under Other Agreements

the licences granted under the Synaptech-Janssen Licence Agreement and/or the Shire-Janssen Sub-licence Agreement are finally terminated provided that if only the licences granted under one of the aforementioned agreements are terminated then Shire shall have the option to cancel Janssens rights and licences under this Agreement in respect of the countries covered by the licence agreement which has been terminated. For the avoidance of doubt this Clause 23.2.4 shall not apply if Janssen terminates Synaptech-Janssen Licence Agreement and/or the Shire-Janssen Sub-licence Agreement but retains the licences and rights granted under such agreements.

23.3 Termination by Janssen

Janssen may terminate this Agreement and the licences granted in Clause 2 without cause by giving Shire 90 days notice of termination on or after 1st January 1996.

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24.1.7 Data, Studies and Product Approvals

Janssen shall free of charge promptly transfer to Shire or its designated Affiliates:-

24.1.7.1 all Development Data and other information arising out of or in connection with the development work conducted by or on behalf of Janssen or its Affiliates pursuant to this Agreement; and

24.1.7.2 all Product Approvals and any applications therefore in the Shire Territory; and

24.1.7.3 any ongoing development work in relation to the Licensed Product and the management of any studies forming part of the Development Plan being carried out by or on behalf of Janssen or its Affiliates at the date of termination; and

24.1.7.4 the International Registration File.

24.1.8 Ownership of Data

24.1.8.1 All Development Data, the International Registration File and other information generated by or on behalf of Janssen in relation to the Licensed Product shall become wholly owned by Shire. Janssen shall free of charge execute such instruments as are reasonably required by Shire to transfer to Shire Janssen's share of the ownership in the Development Data, and the International Registration File.

24.1.8.2 Shire shall have the exclusive right to use the Development Data and the International Registration File in connection with Alzheimer's disease and related dementias in the Shire Territory and the United Kingdom and the Republic of Ireland and Synaptech shall have the exclusive right to use the Development Data in connection with Alzheimer's disease and related dementias in the Janssen Territory.

24.1.8.3 Shire shall have the exclusive worldwide right to use the Development Data and the International Registration File in connection with all indications other than Alzheimer's disease and related dementias.

24.1.8.4 Janssen shall not use the Development Data and/or the International Registration File for any purpose (other than for internal research purposes) or disclose it to any third party.

24.1.9 Janssen's Manufacturing Intellectual Property

Janssen shall grant to Shire free of all charges a non-exclusive, royalty-free, irrevocable worldwide licence under all intellectual property rights of Janssen and its Affiliates which are necessary or useful for the manufacture of Synthetic Galanthamine together with the right to grant sub-licences thereunder for the purposes of manufacturing Synthetic Galanthamine.

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24.2 Sharing of Development Payments

If Janssen properly terminates this Agreement in accordance with Clause 23.3 then in addition to Clause 24.1 above Shire may at its sole discretion either continue the Co-Development Plan at its own cost or commence the winding down of such studies that are on-going thereunder in the following manner:

24.2.1 Janssen, Shire or any relevant third party (as the case may be) shall finalise any pre-clinical studies (which for the avoidance of doubt excludes any carcinogenicity study) that have been commenced or initiated under the Co-Development Plan prior to the date of termination and for a period of 3 months from the date of termination the costs incurred shall be divided in the proportions 97.5% Janssen and 2.5% Shire.

24.2.2 Janssen, Shire or any relevant third party shall continue any carcinogenicity study that has been commenced or initiated under the Co-Development Plan prior to the date of termination for a period of at least 3 months after this date and for that 3 month period from the date of termination the costs incurred shall be divided in the proportions 97.5% Janssen and 2.5% Shire.

24.2.3 Janssen, Shire or any relevant third party shall continue any clinical studies commenced or initiated under the Co-Development Plan prior to the date of termination until either the first point at which or the least expensive method by which these studies can be ethically terminated. The parties shall agree the point at which this can be achieved in the period after Janssen serves notice of termination on Shire and prior to the effective date of termination. The costs incurred from the date of termination in connection therewith shall be divided in the proportions 97.5% Janssen and 2.5% Shire.

24.2.4 Shire may wish to continue any or all of the studies referred to in Clauses 24.2.1 to 24.2.3 above and may require Janssen to complete or procure the completion of a particular study after the agreed date for termination of such study provided that Shire shall be solely responsible for the costs thereof which shall be determined in accordance with either (1) the costs and timelines set out in the Co-Development Plan and the Cost Development Plan or (2) if the study is being carried out by a third party the costs and timelines set out in the contract with such third party.

24.2.5 Shire shall invoice Janssen for the sums to be paid by Janssen under this Clause 24.2 as and when such development costs are incurred by Shire. Payment shall be due within 30 days of the date of any such invoice.

24.3 Consequences of termination by Janssen for Material Breach

If this Agreement is terminated by Janssen for material breach by Shire pursuant to Clause 23.1.1 then from the date of such termination Shire and Janssen shall meet to agree minimal conditions for Janssen to use, the Manufacturing Intellectual Property Rights and the Chiroscience Intellectual Property Rights subject to the provisions of the Chiroscience Agreement. Such conditions shall include without limitation the payment of 50% of the royalties otherwise due under Clause 6.1 and the provisions of Clauses 6, 7 and 8.

24.4 Termination of Related Agreements

If this Agreement shall terminate for any reason (other than termination by Janssen for material breach by Shire pursuant to Clause 23.1.1) then Shire shall have the option to require Janssen to give notice of termination without cause under either or both of the Shire-Janssen Sub-licence Agreement and the Synaptech-Janssen Licence Agreement.

25. Cancellation Of Licences

Without prejudice to any other right or remedy Shire may have, Shire shall be entitled to cancel the licences granted in Clause 2 and those granted pursuant to Clause 2 of the Shire-Janssen Sub-licence Agreement in respect of a particular Major Country or Major Countries in accordance with the following provisions:-

25.1 Lack of Reasonable Efforts

If in respect of any Major Country Janssen is in breach of its obligations under Clauses 9.2.3, 9.2.4, 9.3.3 and/or 9.3.6 and Janssen fails to rectify such breach within 3 months of Shire having notified Janssen of such breach then Shire may cancel Janssens licences for such Major Country on 30 days notice. Any dispute as to whether Janssen, has failed to rectify any such breach of Clauses 9.2.3, 9.2.4, 9.3.3 and/or 9.3.6 shall be referred to arbitration pursuant to Clause 28.12.

25.2 Discontinuation of Sale

If Janssen after having launched the Licensed Product in a Major Country discontinues sale of the Licensed Product in such Major Country for a period of six months or more for reasons other than Force Majeure as defined in Clause 27 and fails to resume sales in such country within 30 days of having been notified of such failure by Shire then Shire may cancel Janssen's licences in such Major Country forthwith. For the purpose of this Clause 25.2 sales of minimal, commercially insignificant quantities of Licensed Product shall be deemed to constitute a discontinuation of sales.

25.3 Cancellation of the Licences granted under the other Agreements

If the licences granted to Janssen under the Synaptech-Janssen Licence or the Shire-Janssen Sub-licence Agreement shall finally terminate in respect of any Major Country or Major Countries then Shire shall have the option to cancel Janssen's licences in respect of the same country or countries under this Agreement by giving Janssen immediate notice of cancellation.

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26. **Consequences Of Cancellation Of Licence**

Upon cancellation of the licences granted under Clause 2 in respect of any Major Country of the Territory pursuant to Clause 19, Clause 20 and/or Clause 25:-

26.1 Janssen shall at Shire's direction take all necessary steps to arrange for the transfer of :-

26.1.1 the Product Approvals (or applications therefor) in such country into Shire's name or the name of any third party designated by Shire for such purposes; and

26.1.2 any trade marks and registrations or applications therefor used in connection with the Licensed Product in such country to Shire and Janssen shall promptly free of charge execute assignments in the form reasonably requested by Shire to transfer such trade marks, registrations and/or application in such country to Shire or a designated Affiliate of Shire together with all goodwill associated with such trade marks in such country.

26.2 Janssen shall be entitled to continue to sell existing stocks of the Licensed Product in such country for an agreed period of not longer than 6 months following the date of cancellation provided that Janssen pays to Shire the royalties due in respect of such sales in accordance with the provisions of this Agreement. The parties shall use all reasonable endeavours to ensure that a smooth transfer of the Licensed Product in such country takes place.

26.3 The definitions of Shire Territory, Janssen Territory and Territory contained in this Agreement shall be deemed amended so as to exclude such country.

26.4 Without prejudice to the provisions of the Synaptech-Janssen Licence Agreement Shire shall have the exclusive right to use the Development Data and the Ciba Data in such country.

27. **Force Majeure**

27.1 Neither party shall terminate this Agreement or be liable to the other under this Agreement for loss or damages attributable to any act of God, earthquake, flood, fire, explosion, strike, lockout, labour dispute, casualty or accident, war, revolution, civil commotion, act of public enemies, blockage or embargo, injunction, law, order, proclamation, regulation, ordinance, demand or requirement of any government or subdivision, authority (including, without limitation, regulatory authorities) or representatives of any such government, or any other cause beyond the reasonable control of such party, if the party affected shall give prompt notice of any such cause to the other party. The party giving such notice shall thereupon be excused from such of its obligations hereunder as it is so disabled during, but no longer than the existence of such cause.

27.2 If such cause continues unabated for a period of at least 90 days, both parties will meet to discuss what, if any, modifications should be made to this Agreement as a consequence of such Force Majeure.

28. Miscellaneous

28.1 Performance by Affiliates

The parties may perform some or all of their obligations under this Agreement through their Affiliates and Business Partners provided that each party shall remain solely responsible for and be guarantor of the performance by its Affiliates and Business Partners and procure that its Affiliates and Business Partners comply fully with the provision of this Agreement in connection with such performance.

28.2 Severance

If any provision of this Agreement is held to be invalid or inapplicable by a court of competent jurisdiction the remaining provisions will continue in full force and the parties will make such amendments to this Agreement by the addition or deletion of wording as appropriate to remove the invalid or unenforceable part of such provision but otherwise achieve to the maximum extent permissible, the economic, legal and commercial objectives of the original provision.

28.3 Waiver

Failure or delay by either party in exercising or enforcing any right or remedy under this Agreement in whole or in part shall not be deemed a waiver thereof or prevent the subsequent exercise of that or any other rights or remedy.

28.4 Headings

The headings in this Agreement are for convenience only and shall not affect its interpretation.

28.5 Assignment

Subject to Clause 28.1 neither Shire nor Janssen shall assign, transfer, sub-licence, sub-contract, mortgage, charge or otherwise make over to any third party any of its rights or obligations under this Agreement without the prior written consent of the other party. Prior to any such transaction the party wishing to effect the transaction shall procure that the third party concerned covenants directly with the other party to this Agreement to comply with all the provisions of this Agreement.

28.6 No Agency

Except as expressly stated in this Agreement, neither party shall act or describe itself as the agent of the other nor shall it make, or represent that it has authority to make, any commitments on the other's behalf.

28.7 Notices

28.7.1 Any notice or other document given under this Agreement shall be in writing in the English language and shall be given by hand or sent by prepaid airmail or by facsimile transmission to the address of the receiving party as set out in Clauses 28.7.3 and 28.7.4 below unless a different address or facsimile number has been notified to the other in writing for this purpose.

28.7.2 Each such notice or document shall:-

28.7.2.1 if sent by hand, be deemed to have been given when delivered at the relevant address;

28.7.2.2 if sent by prepaid airmail, be deemed to have been given 3 days after posting; and

28.7.2.3 if sent by facsimile transmission, be deemed to have been given when transmitted provided that a confirmatory copy of such facsimile transmission shall have been sent by prepaid airmail within 24 hours of such transmission.

28.7.3 Shire's address for service of notices and other documents shall be:-

For the attention of:
The Directors
Shire International Licensing BV
Frederiksplein 42
1017 XN
Amsterdam
The Netherlands
Facsimile No: 31 20 55 33 777

A copy of each such notice shall be sent simultaneously to:

The Directors
Shire Pharmaceutical Group Plc
East Anton
Andover
Hampshire
SP10 5RG
England
Fax No: 44 1264 334657

28.7.4 Janssen's address for service of notices and other documents shall be:-

For the attention of:
The International Vice President of Business Development
Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium
Facsimile No: 32 14 60 50 25

28.7.5 Janssen shall notify Shire forthwith with a copy of any notices sent or received pursuant to the Synaptech-Janssen Licence Agreement.

28.8 Entire Agreement

28.8.1 This Agreement, the Shire-Janssen Sub-licence Agreement, the two side letters of the same date as this Agreement one from Synaptech to Shire Holdings Limited, Shire and Janssen and the other from Shire to Janssen constitute the entire agreement and understanding of the parties relating to the subject matter of this Agreement and supersede all prior oral or written agreements, understandings or arrangements between them relating to such subject save for the confidentiality agreement dated 24 February 1995 between Janssen and Shire Pharmaceutical Development Limited which shall remain in full force and effect.

28.8.2 The parties acknowledge that they are not relying on any agreement, understanding, arrangement, warranty, representation or term which is not set out in this Agreement.

28.8.3 No change or addition may be made to this Agreement except in writing signed by the duly authorised representatives of both parties.

28.8.4 The parties irrevocably and unconditionally waive any rights and/or remedies they may have (including without limitation the right to claim damages and/or to rescind this Agreement) in respect of any misrepresentation other than a misrepresentation which is contained in this Agreement or a misrepresentation which was made fraudulently.

28.8.5 Nothing in this Clause 28.8 shall operate to:

28.8.5.1 exclude any provision implied into this Agreement by law and which may not be excluded by law; or

28.8.5.2 limit or exclude any liability, right or remedy to a greater extent than is permissible under law.

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28.9 Compliance with Local Requirements

If in any jurisdiction the effect of any provision(s) of this Agreement or the absence from this Agreement of any provision(s) would be to prejudice the Patents or any remedy under the Patents, the parties will make such amendments to this Agreement and execute such further agreements and documents limited to that part of the Territory which falls under such jurisdiction as may be necessary to remove such prejudicial effects.

28.10 Publicity

In the absence of specific agreement between the parties, neither party shall originate any publicity, news release or public announcement, written or oral, whether to the public or press, relating to this Agreement including its existence, the subject matter to which it relates, performance under it or any of its terms, to any amendment hereto save only such announcement as in the opinion of counsel for the party making such announcement is required by law to be made. Any such announcements shall be factual and as brief as possible. If a party decides to make an announcement required by law, it will give the other party thirty (30) days advance written notice, where possible, of the text of the announcement so that the other party will have an opportunity to comment upon the announcement.

28.11 Law

This Agreement is made under English law.

28.12 Disputes

28.12.1 Subject to Clauses 28.12.2 and 28.13 any disputes relating to this Agreement of whatever nature that cannot be resolved by negotiation between the parties shall be referred for final resolution to arbitration in London by a single Arbitrator under the Rules of the Chartered Institute of Arbitrators. The decision of the arbitrator shall be final and binding upon the parties and their legal successors. The arbitrator may at his discretion, provide for discovery by the parties not to exceed 4 months from the date of notice of arbitration and the arbitrator shall notify the parties of his decision in writing within 30 days of the completion of the final hearing and may at his discretion award costs and expenses in respect of the arbitration but shall not award punitive damages.

28.12.2 The parties submit to the exclusive jurisdiction of the English courts in respect of any breach of the provisions of Clauses 3.1 and/or 3.2 and/or any persistent breach of the provisions of Clauses 6.1 and 6.2.

28.13 Expert

Where this Agreement provides that a dispute shall or may be referred to an expert for resolution then such dispute shall be decided in accordance with the provisions set out in Schedule 8.

Agreed by the parties through their duly authorised representatives:-

For and on behalf of Shire International Licensing BV:

Signed: .....

Name: L J M Rijnsburg

Title: Managing director

Signed: .....

Name: D. M. Ruhdeerkamp

Title: Managing Director

For and on behalf of Janssen Pharmaceutical N.V.

Signed: .....

Name: G. Van Reet

Title: Managing Director

Signed: .....

Name: A. Shetty

Title: Executive Vice President

EXHIBIT 67

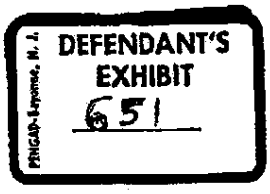
GALANTHAMINE FOR ALZHEIMER'S DISEASE

Galanthamine hydrobromide is a centrally-acting acetylcholinesterase inhibitor with pharmacologic properties that are ideally suited for the treatment of Alzheimer's disease. It is theoretically capable of producing a greater therapeutic effect in Alzheimer's disease than has been observed with other agents.

The cholinergic defect in Alzheimer's disease is universal, involves the majority of brain acetylcholine, and correlates with the histopathology and the degree of dementia.(1-4) Predictably, the vast majority of studies with drugs that increase cerebral cholinergic activity have shown mild to moderate improvement in a substantial proportion of patients.(5) Indeed, the Alzheimer's brain, even at autopsy, is able to produce normal amounts of acetylcholine after treatment with physostigmine in vitro.(6) It would be imprudent to ignore the well-established abnormalities of the cerebral cholinergic systems in Alzheimer's dementia. Restoration of secondary neurochemical deficits may play a role in certain cases, but it is quite improbable that brain function in Alzheimer's disease will be improved without effective restitution of its cholinergic deficit, a first step in any ultimate pharmacotherapy. When cholinergic therapies have produced less substantial results than desired, a critical evaluation of the therapies themselves reveals that the drugs used have often been incapable of increasing brain acetylcholine.

Physostigmine, one of the most effective of the agents employed, reaches erratic plasma levels, has a short (15 min) plasma half-life, and penetrates the blood brain barrier poorly.(7,8) The variability in plasma levels is presumably due to enzymatic hydrolysis in plasma and is so great that 20-fold differences in plasma concentrations have been reported following 2 mg oral doses given to different subjects.(9,10) At peak plasma levels, brain concentrations are half of those in plasma.(7) Thus, pronounced peripheral activity has often accompanied minimal central activity, and side effects have have limited tolerated doses of physostigmine.(11)

When methods have been devised to assess the inhibition of cholinesterase achieved inside the blood brain barrier by physostigmine, it has been clear that cognitive effects have been strongly correlated with other evidence of central activity of physostigmine. Specifically, stimulation of plasma cortisol, which occurs via central cholinergic synapses, correlates highly (r=.88) with improvement in Alzheimer's symptoms.(12)



Measurement of cholinesterase inhibition in CSF, also reflecting physostigmine's penetration of the blood brain barrier, correlates with the cognitive response as well.(11) The number of characteristic intrusion errors decreased as physostigmine was shown to have increased effect in CSF (r=.95). Even tetrahydroaminoacridine (THA), which has recently produced substantial improvement in Alzheimer's patients, was only minimally effective until a plasma assay demonstrated the need for much higher doses in many patients. (13,14)

Inadequate plasma levels, lack of inhibition of enzyme, and the absence of centrally-mediated neuroendocrine activity have accompanied therapeutic failure. Conversely, ascertainment of adequate drug concentrations in plasma, direct demonstration of cholinesterase inhibition in CSF, and stimulation of the hypothalamic-pituitary adrenal axis have accompanied effective augmentation of central cholinergic activity, and paralleled cognitive enhancement. These separate lines of evidence all indicate that when adequate cholinesterase inhibition is achieved in brain, therapeutic effects of acetylcholinesterase inhibitors are seen in Alzheimer's disease.

Galanthamine is a potent cerebral cholinesterase inhibitor. Intraperitoneal injection of 4 mg/kg in mice results in 75% inhibition of brain cholinesterase at 30 minutes, 38% inhibition remains at 150 minutes.(15) Centrally-mediated neuroendocrine effects of a clinical dose of galanthamine in humans persist for a minimum of six hours.(16) Effective inhibition of brain cholinesterase is confirmed in behavioral experiments in mice, in whom scopolamine-induced amnesia is reversed by galanthamine at a dose of 1 mg/kg.(17) In a separate report, employing 5 mg/kg, galanthamine reversed scopolamine's inhibition of learning and dilated constricted pial arteries.(18) These behavioral experiments indicate that galanthamine, administered peripherally, is clearly effective within the central nervous system. Thus, the central cholinergic activity of galanthamine is demonstrated biochemically, using a "neuroendocrine window," and in classical pharmacological paradigms.

The pharmacokinetic properties of galanthamine permit straightforward administration with a minimum of side effects. Bioavailability after oral administration is 65%; peak plasma concentrations are reached at 15-20 minutes.(19) Galanthamine is highly selective for brain. Brain concentrations are 3.25x higher than peak plasma levels.(19) In comparison, physostigmine brain levels are 0.48x peak plasma concentrations, as cited above.(7) This difference in brain:body partitioning predicts a much higher ratio of central cholinergic enhancement to peripheral side effects for galanthamine than for physostigmine. Thus, while physostigmine should be the drug of choice to counter the cardiac effects of tricyclic antidepressants, galanthamine would be a better selection for the reversal of the central cholinergic deficit of Alzheimer's disease.

Galanthamine is resistant to degradation by plasma hydrolases. Plasma concentrations are therefore proportional to the administered doses and galanthamine appears to follow linear kinetic behavior.(20) Plasma levels are predictable: 8 patients receiving 0.3 mg/kg IV had a mean ± SE plasma concentration of 128 ± 14 ng/ml at 30 minutes. The elimination half-life is 264±28 min in humans.(20) THA, by contrast, is capricious in its pharmacokinetics. Several patients receiving the highest allowed dose of THA, 150 mg/day, were found to have negligible plasma levels when a sensitive plasma assay was developed. In fact, the success of THA in this report, in contrast to the modest results obtained previously, was largely attributed to this assay, enabling adequate THA doses to be ascertained and administered to all patients. As cited above, physostigmine similarly demonstrates a

> "nonlinear relation between the size of the dose and the amount excreted in urine, which suggests saturable presystemic metabolism. Since individual patients will probably vary in the degree of this presystemic metabolism, the same dose of oral physostigmine could produce sub-threshold levels in one patient and unwanted effects in another."(10)

Such data "underscore the importance of measuring plasma physostigmine concentrations in studies of the clinical efficacy of oral physostigmine treatment in Alzheimer's disease."(9) In contrast to physostigmine and THA, galanthamine's ready bioavailability, resistance to plasma hydrolases and predictable plasma levels, make it unlikely that blood tests for drug levels will be necessary in routine clinical practice.

In practice, galanthamine has been well-tolerated at doses which have shown the neuroendocrine effects described above. From a series of 2853 patients given 10-40 mg IV push, it is stated that,

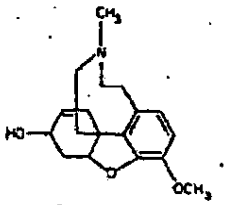
> "Many of our patients had serious heart conditions. Therefore from the very beginning of our tests we studied the effect of galanthamine in 40 patients with hypoxia of the myocardium and myocardial lesions. The cardiac activity and its rhythm remained unchanged on decurarization with Nivalin..." [Galanthamine does produce the expected cholinergic effects on cardiac rhythm, but these would not be expected to be clinically significant in many cases, particularly as the doses that would be used for Alzheimer's disease would be lower than those used in anesthesia.]..."Most of our patients were older than 60 years. Old people endure well the decurarization with galanthamine...Apart from patients with heart conditions, Nivalin was applied also to patients with diabetes and kidney diseases...No damage to the liver, water-mineral balance, and uropoeisis, or hematopoesis were established due to the application of galanthamine."(21)

The author of a second series, comprising 650 patients, states:

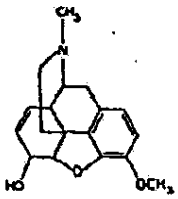
> "A large therapeutic margin, good tolerance, and reliable action are its main advantages... it has a long lasting effect which comes on gradually. It is very useful in decurarization of adults and children, even in very ill patients... Since the muscarinic effect of the drug is small, no atropine need be given prior to the decurarization. In the case of bradycardia, however, the administration of atropine is recommended if larger doses of galanthamine have to be used."(22)

As of 1967, 6000 patients had received the drug at Sophia University Hospital alone.(23) Recent publications indicate that galanthamine continues to be used for the reversal of neuromuscular blockade. Thus, galanthamine has remained clinically acceptable for 25 years.

Serious chemical toxicity would not be anticipated from a compound of this class. Galanthamine is a natural alkaloid initially isolated from the Bulgarian snowdrop, Nivalus galanthus, but is present in greater amounts in Narcissus hybridus. (23-25) It is widely distributed among plant species, including daffodils. (26-33)



galanthamine



codeine

As a phenanthrene sharing close structural similarity with codeine and morphine, galanthamine belongs to a group of compounds with extensive and longstanding clinical experience, and minimal toxicity. A marked contrast exists between galanthamine as a phenanthrene and THA as a 9-aminoacridine in this regard. The 9-aminoacridines bind strongly to DNA and intercalate themselves into the DNA template. By yet another mechanism, they can totally inhibit transcription of DNA by RNA polymerases of higher organisms.(34) 9-aminoacridines are currently being developed as antineoplastic agents and abortifacients.(35) Impairment of wound healing, hepatic and hematologic toxicity have been reported.(36,37) Thus, while galanthamine and THA are identical in their effects on brain acetylcholinesterase, galanthamine is likely to be safer on chemical grounds. Safety may be important as patients with less advanced disease are exposed to the compound for longer periods, and in combination with other agents and therapies which they may receive.

Thus, galanthamine appears to preferable to other anticholinesterases because it is well-absorbed, reaches predictable plasma levels, partitions selectively to brain, is characterized by a reasonable duration of action, good tolerance, and a relatively nontoxic chemical background. Fundamental research in Alzheimer's disease confirms a universal cholinergic deficit which correlates with plaque counts and mental test scores. Fundamental pharmacologic data indicate that agents which failed to significantly ameliorate the symptoms of Alzheimer's disease probably did not reverse the cholinergic deficit in brain. Galanthamine has the pharmacological and clinical properties to reverse the cholinergic deficit in Alzheimer's disease.

References

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2. Davies P, Maloney AJF (1976) Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet ii:1403

3. Perry EK, Perry RH, Blessed G, Tomlinson BE (1977) Necropsy evidence of central cholinergic deficits in senile dementia. Lancet i:189

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EXHIBIT 68

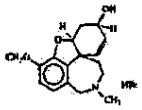
Razadyne ER
galantamine HBr
EXTENDED-RELEASE CAPSULES

Razadyne
galantamine HBr
Tablets and Oral Solution

7517314
01RZ291A

DESCRIPTION

RAZADYNE® ER/RAZADYNE® (galantamine hydrobromide) is galantamine hydrobromide, a reversible, competitive acetylcholinesterase inhibitor. Galantamine hydrobromide is known chemically as (4aS,6R,8aS)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol hydrobromide. It has an empirical formula of $C_{17}H_{21}NO_3 \cdot HBr$ and a molecular weight of 368.27. Galantamine hydrobromide is a white to almost white powder and is sparingly soluble in water. The structural formula for galantamine hydrobromide is:



RAZADYNE® ER is available in opaque hard gelatin extended-release capsules of 8 mg (white), 16 mg (pink), and 24 mg (caramel) containing galantamine hydrobromide, equivalent to respectively 8, 16 and 24 mg galantamine base. Inactive ingredients include gelatin, diethyl phthalate, ethylcellulose, hypromellose, polyethylene glycol, titanium dioxide and sugar spheres (sucrose and starch). The 16 mg capsule also contains red ferric oxide. The 24 mg capsule also contains red ferric oxide and yellow ferric oxide.

RAZADYNE® for oral use is available in circular biconvex film-coated immediate-release tablets of 4 mg (off-white), 8 mg (pink), and 12 mg (orange-brown). Each 4, 8, and 12 mg (base equivalent) tablet contains 5.126, 10.253, and 15.379 mg of galantamine hydrobromide, respectively. Inactive ingredients include colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, propylene glycol, talc, and titanium dioxide. The 4 mg tablets contain yellow ferric oxide. The 8 mg tablets contain red ferric oxide. The 12 mg tablets contain red ferric oxide and FD&C yellow #6 aluminum lake.

RAZADYNE® is also available as a 4 mg/mL oral solution. The inactive ingredients for this solution are methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium saccharin, sodium hydroxide and purified water.

CLINICAL PHARMACOLOGY

Mechanism of Action

Although the etiology of cognitive impairment in Alzheimer's disease (AD) is not fully understood, it has been reported that acetylcholine-producing neurons degenerate in the brains of patients with Alzheimer's disease. The degree of this cholinergic loss has been correlated with degree of cognitive impairment and density of amyloid plaques (a neuropathological hallmark of Alzheimer's disease).

Galantamine, a tertiary alkaloid, is a competitive and reversible inhibitor of acetylcholinesterase. While the precise mechanism of galantamine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this mechanism is correct, galantamine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that galantamine alters the course of the underlying dementing process.

Pharmacokinetics

Galantamine is well absorbed with absolute oral bioavailability of about 90%. It has a terminal elimination half-life of about 7 hours and pharmacokinetics are linear over the range of 8-32 mg/day.

The maximum inhibition of acetylcholinesterase activity of about 40% was achieved about one hour after a single oral dose of 8 mg galantamine in healthy male subjects.

Absorption and Distribution

Galantamine is rapidly and completely absorbed with time to peak concentration about 1 hour. Bioavailability of the tablet was the same as the bioavailability of an oral solution. Food did not affect the AUC of galantamine but C_{max} decreased by 25% and T_{max} was delayed by 1.5 hours. The mean volume of distribution of galantamine is 175 L.

The plasma protein binding of galantamine is 18% at therapeutically relevant concentrations. In whole blood, galantamine is mainly distributed to blood cells (52.7%). The blood to plasma concentration ratio of galantamine is 1.2.

Metabolism and Elimination

Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated, and excreted unchanged in the urine. *In vitro* studies indicate that cytochrome CYP2D6 and CYP3A4 were the major cytochrome P450 isoenzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly (see PRECAUTIONS, Drug-Drug Interactions). O-demethylation, mediated by CYP2D6 was greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity.

In studies of oral ^{3}H-galantamine, unchanged galantamine and its glucuronide, accounted for most plasma radioactivity in poor and extensive CYP2D6 metabolizers. Up to 8 hours post-dose, unchanged galantamine accounted for 39-77% of the total radioactivity in the plasma, and galantamine glucuronide for 14-24%. By 7 days, 93-99% of the radioactivity had been recovered, with about 95% in urine and about 5% in the feces. Total urinary recovery of unchanged galantamine accounted for, on average, 32% of the dose and that of galantamine glucuronide for another 12% on average.

After i.v. or oral administration, about 20% of the dose was excreted as unchanged galantamine in the urine in 24 hours, representing a renal clearance of about 65 mL/min, about 20-25% of the total plasma clearance of about 300 mL/min.

RAZADYNE® ER 24 mg Extended-Release Capsules administered once daily under fasting conditions are bioequivalent to RAZADYNE® Tablets 12 mg twice daily with respect to AUC_{ss} and C_{max}. The C_{max} and T_{max} of the extended-release capsules were lower and occurred later, respectively, compared with the immediate-release tablets, with C_{max} about 25% lower and median T_{max} occurring about 4.5 – 5.0 hours after dosing. Dose-proportionality is observed for RAZADYNE® ER Extended-Release Capsules over the dose range of 8 to 24 mg daily and steady state is achieved within a week. There was no effect of age on the pharmacokinetics of RAZADYNE® ER Extended-Release Capsules. CYP2D6 poor metabolizers had drug exposures that were approximately 50% higher than for extensive metabolizers.

There are no appreciable differences in pharmacokinetic parameters when RAZADYNE® ER Extended-Release Capsules are given with food compared to when they are given in the fasted state.

Special Populations

CYP2D6 Poor Metabolizers

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar C_{max} and about 35% AUC$_\infty$ increase of unchanged galantamine compared to extensive metabolizers.

A total of 356 patients with Alzheimer's disease enrolled in two Phase 3 studies were genotyped with respect to CYP2D6 (n=218 hetero-extensive metabolizers, 126 homo-extensive metabolizers, and 20 poor metabolizers). Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability.

Hepatic Impairment:

Following a single 4 mg dose of galantamine tablets, the pharmacokinetics of galantamine in subjects with mild hepatic impairment (n=8; Child-Pugh score of 5-6) were similar to those in healthy subjects. In patients with moderate hepatic impairment (n=8; Child-Pugh score of 7-9), galantamine clearance was decreased by about 25% compared to normal volunteers. Exposure would be expected to increase further with increasing degree of hepatic impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Impairment:

Following a single 8 mg dose of galantamine tablets, AUC increased by 37% and 67% in moderate and severely renal-impaired patients compared to normal volunteers (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly:

Data from clinical trials in patients with Alzheimer's disease indicate that galantamine concentrations are 30-40% higher than in healthy young subjects.

Gender and Race:

No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of RAZADYNE®, but a population pharmacokinetic analysis indicates (n= 539 males and 550 females) that galantamine clearance is about 20% lower in females than in males (explained by lower body weight in females) and race (n= 1029 White, 24 Black, 13 Asian and 23 other) did not affect the clearance of RAZADYNE®.

Drug-Drug Interactions (see also PRECAUTIONS, Drug-Drug Interactions)

Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine so no single pathway appears predominant. Based on *in vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine. CYP2D6 was involved in the formation of O-desmethyl-galantamine, whereas CYP3A4 mediated the formation of galantamine-N-oxide. Galantamine is also glucuronidated and excreted unchanged in urine.

(A) Effect of Other Drugs on the Metabolism of RAZADYNE®:

Drugs that are potent inhibitors of CYP2D6 or CYP3A4 may increase the AUC of galantamine. Multiple dose pharmacokinetic studies demonstrated that the AUC of galantamine increased 30% and 40%, respectively, during co-administration of ketoconazole and paroxetine. As co-administered with erythromycin, another CYP3A4 inhibitor, the galantamine AUC increased only 10%. Population PK analysis with a database of 852 patients with Alzheimer's disease showed that the clearance of galantamine was decreased about 25-33% by concurrent administration of amitriptyline (n = 17), fluoxetine (n = 48), fluvoxamine (n = 14), and quinidine (n = 7), known inhibitors of CYP2D6.

Concurrent administration of H_2-antagonists demonstrated that ranitidine did not affect the pharmacokinetics of galantamine, and cimetidine increased the galantamine AUC by approximately 16%.

A multiple dose pharmacokinetic study with concurrent administration of memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, demonstrated that co-administration of memantine in a dose of 10 mg BID did not affect the pharmacokinetic profile of galantamine (16 mg daily) at steady state.

(B) Effect of RAZADYNE® on the Metabolism of Other Drugs:

In vitro studies show that galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 and CYP2E1. This indicated that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low. Multiple doses of galantamine (24 mg/day) had no effect on the pharmacokinetics of digoxin and warfarin (R- and S- forms). Galantamine had no effect on the increased prothrombin time induced by warfarin.

CLINICAL TRIALS

The effectiveness of RAZADYNE® ER/RAZADYNE® (galantamine hydrobromide) as a treatment for Alzheimer's disease is demonstrated by the results of 5 randomized, double-blind, placebo-controlled clinical investigations in patients with probable Alzheimer's disease, 4 with the immediate-release tablet and 1 with the extended-release capsule (diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination scores that were ≥10 and ≤ 24). Doses studied with the tablet formulation were 8-32 mg/day given as twice daily dose. In 3 of the 4 studies with the tablet, patients were started on a low dose of 8 mg, then titrated weekly by 8 mg/day to 24 or 32 mg as assigned. In the fourth study (USA 4-week Dose-Escalation Fixed-Dose Study) dose escalation of 8 mg/day occurred over 4 week intervals. The mean age of patients participating in these 4 RAZADYNE® trials was 75 years with a range of 41 to 100. Approximately 62% of patients were women and 38% were men. The racial distribution was: White 94%, Black 3% and other races 3%. Two other studies examined a three times daily dosing regimen; these also showed or suggested benefit but did not suggest an advantage over twice daily dosing.

Study Outcome Measures:

In each study, the primary effectiveness of RAZADYNE® was evaluated using a dual outcome assessment strategy as measured by the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Impression of Change that required the use of caregiver information (CIBIC-plus).

The ability of RAZADYNE® to improve cognitive performance was assessed with the cognitive sub-scale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The patients recruited as participants in each study using the tablet formulation had mean scores on ADAS-cog of approximately 27 units, with a range from 5 to 68. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's disease suggests that they gain 6 to 12 units a year on the ADAS-cog. Lesser degrees of change, however, are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in RAZADYNE® trials was approximately 4.5 units per year.

The ability of RAZADYNE® to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC-plus. The CIBIC-plus is not a single instrument and is not a standardized instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC-plus evaluations from other clinical trials. The CIBIC-plus used in the trials was a semi-structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of 4 major areas of patient function: general, cognitive, behavioral and activities of daily living. It represents the assessment of a skilled clinician based on his/her observation at an interview with the patient, in combination with information supplied by a caregiver familiar with the behavior of the patient over the interval rated. The CIBIC-plus is scored as a seven point categorical rating, ranging from a score of 1, indicating "markedly improved," to a score of 4, indicating "no change" to a score of 7, indicating "marked

worsening." The CIBIC-plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

Immediate-Release Tablets

U.S. Twenty-One Week Fixed-Dose Study

In a study of 21 weeks duration, 978 patients were randomized to doses of 8, 16, or 24 mg of RAZADYNE® per day, or to placebo, each given in 2 divided doses. Treatment was initiated at 8 mg/day for all patients randomized to RAZADYNE®, and increased by 8 mg/day every 4 weeks. Therefore, the maximum titration phase was 8 weeks and the minimum maintenance phase was 13 weeks (in patients randomized to 24 mg/day of RAZADYNE®).

Effects on the ADAS-cog:

Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all four dose groups over the 21 weeks of the study. At 21 weeks of treatment, the mean differences in the ADAS-cog change scores for the RAZADYNE®-treated patients compared to the patients on placebo were 1.7, 3.3, and 3.6 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo and to the 8 mg/day treatment. There was no statistically significant difference between the 16 mg/day and 24 mg/day dose groups.

Figure 1: Time-Course of the Change From Baseline in ADAS-cog Score for Patients Completing 21 Weeks (5 Months) of Treatment

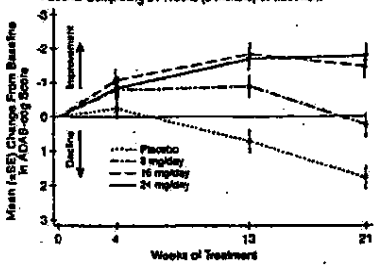
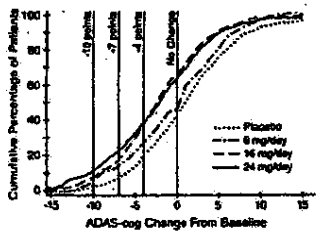


Figure 2 illustrates the cumulative percentages of patients from each of the four treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to galantamine and placebo have a wide range of responses, but that the RAZADYNE® groups are more likely to show the greater improvements.

Figure 2: Cumulative Percentage of Patients Completing 21 Weeks of Double-Blind Treatment With Specified Changes From Baseline in ADAS-cog Scores. The Percentages of Randomized Patients Who Completed the Study Were: Placebo 84%, 8 mg/day 77%, 16 mg/day 78% and 24 mg/day 78%.

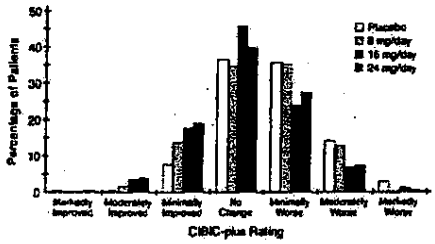


Treatment	Change in ADAS-cog -10	-7	-4	0
Placebo	3.6%	7.6%	19.6%	41.8%
8 mg/day	5.9%	13.9%	25.7%	46.5%
16 mg/day	7.2%	15.9%	35.6%	65.4%
24 mg/day	10.4%	22.3%	37.0%	64.9%

Effects on the CIBIC-plus:

Figure 3 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the four treatment groups who completed 21 weeks of treatment. The RAZADYNE®-placebo differences for these groups of patients in mean rating were 0.15, 0.41 and 0.44 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo. The differences vs. the 8 mg/day treatment for the 16 and 24 mg/day treatments were 0.26 and 0.29, respectively. There were no statistically significant differences between the 16 mg/day and 24 mg/day dose groups.

Figure 3: Distribution of CIBIC-plus Ratings at Week 21



U.S. Twenty-Six Week Fixed-Dose Study

In a study of 26 weeks duration, 636 patients were randomized to either a dose of 24 mg or 32 mg of RAZADYNE® (galantamine hydrobromide) per day, or to placebo, each given in two divided doses. The 26-week study was divided into a 3-week dose titration phase and a 23-week maintenance phase.

Effects on the ADAS-cog:

Figure 4 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the RAZADYNE®-treated patients compared to the patients on placebo were 3.9 and 3.8 units for the 24 mg/day and 32 mg/day treatments, respectively. Both treatments were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 4: Time-Course of the Change From Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

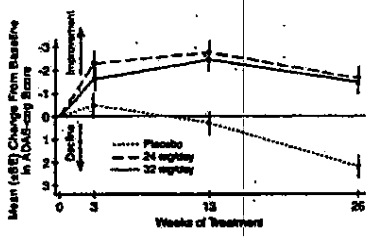
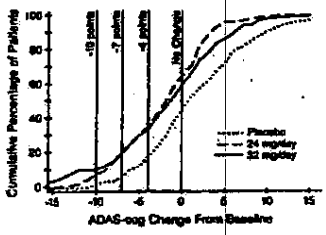


Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to RAZADYNE® and placebo have a wide range of responses, but that the RAZADYNE® groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

Figure 5: Cumulative Percentage of Patients Completing 26 Weeks of Double-Blind Treatment With Specified Changes From Baseline in ADAS-cog Scores. The Percentages of Randomized Patients Who Completed the Study Were: Placebo 81%, 24 mg/day 68%, and 32 mg/day 58%.

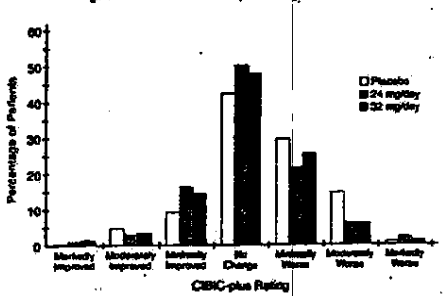


Treatment	Change in ADAS-cog -10	-7	-4	0
Placebo	2.1%	5.7%	16.6%	43.9%
24 mg/day	7.6%	18.3%	33.6%	64.1%
32 mg/day	11.1%	19.7%	33.3%	58.1%

Effects on the CIBIC-plus:

Figure 6 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean RAZADYNE®-placebo differences for these groups of patients in the mean rating were 0.28 and 0.29 units for 24 and 32 mg/day of RAZADYNE®, respectively. The mean ratings for both groups were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 6: Distribution of CIBIC-plus Ratings at Week 26



International Twenty-Six Week Fixed-Dose Study

In a study of 26 weeks duration identical in design to the USA 26-Week Fixed-Dose Study, 653 patients were randomized to either a dose of 24 mg or 32 mg of RAZADYNE® (galantamine hydrobromide) per day, or to placebo, each given in two divided doses. The 26-week study was divided into a 3-week dose titration phase and a 23-week maintenance phase.

Effects on the ADAS-cog:

Figure 7 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the

RAZADYNE®- treated patients compared to the patients on placebo were 3.1 and 4.1 units for the 24 mg/day and 32 mg/day treatments, respectively. Both treatments were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 7: Time-Course of the Change From Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

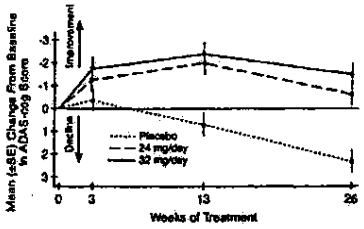
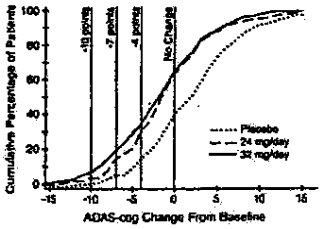


Figure 8 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to RAZADYNE® and placebo have a wide range of responses, but that the RAZADYNE® groups are more likely to show the greater improvements.

Figure 8: Cumulative Percentage of Patients Completing 26 Weeks of Double-Blind Treatment With Specified Changes From Baseline in ADAS-cog Scores. The Percentages of Randomized Patients Who Completed the Study Were: Placebo 67%, 24 mg/day 80%, and 32 mg/day 75%.

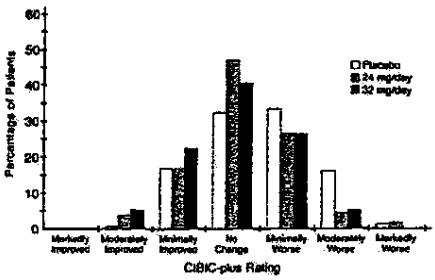


	Change in ADAS-cog			
Treatment	-10	-7	-4	0
Placebo	1.2%	5.8%	15.2%	39.8%
24 mg/day	4.5%	15.4%	30.8%	65.4%
32 mg/day	7.9%	19.7%	34.9%	63.8%

Effects on the CIBIC-plus:

Figure 9 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean RAZADYNE®-placebo differences for these groups of patients in the mean rating of change from baseline were 0.34 and 0.47 for 24 and 32 mg/day of RAZADYNE®, respectively. The mean ratings for the RAZADYNE® groups were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 9: Distribution of CIBIC-plus Rating at Week 26



International Thirteen-Week Flexible-Dose Study

In a study of 13 weeks duration, 386 patients were randomized to either a flexible dose of 24-32 mg/day of RAZADYNE® or to placebo, each given in two divided doses. The 13-week study was divided into a 3-week dose titration phase and a 10-week maintenance phase. The patients in the active treatment arm of the study were maintained at either 24 mg/day or 32 mg/day at the discretion of the investigator.

Effects on the ADAS-cog:

Figure 10 illustrates the time course for the change from baseline in ADAS-cog scores for both dose groups over the 13 weeks of the study. At 13 weeks of treatment, the mean difference in the ADAS-cog change scores for the treated patients compared to the patients on placebo was 1.9. RAZADYNE® at a dose of 24-32 mg/day was statistically significantly superior to placebo.

Figure 10: Time-Course of the Change From Baseline in ADAS-cog Score for Patients Completing 13 Weeks of Treatment

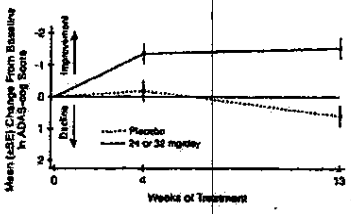
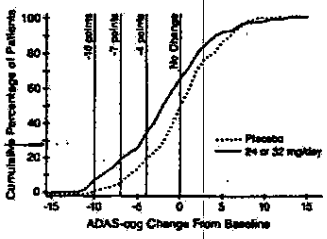


Figure 11 illustrates the cumulative percentages of patients from each of the two treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to RAZADYNE® and placebo have a wide range of responses, but that the RAZADYNE® group is more likely to show the greater improvement.

Figure 11: Cumulative Percentage of Patients Completing 13 Weeks of Double-Blind Treatment With Specified Changes from Baseline in ADAS-cog Scores. The Percentages of Randomized Patients Who Completed the Study Were: Placebo 90%, 24-32 mg/day 87%.

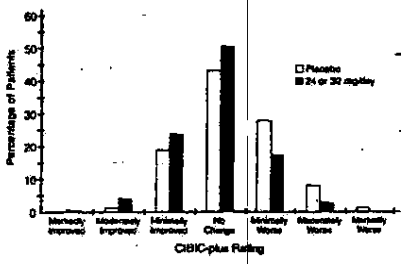


	Change in ADAS-cog			
Treatment	-10	-7	-4	0
Placebo	1.9%	5.6%	19.4%	50.0%
24 or 32 mg/day	7.1%	18.6%	32.9%	65.3%

Effects on the CIBIC-plus:

Figure 12 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the two treatment groups who completed 13 weeks of treatment. The mean RAZADYNE®-placebo differences for the group of patients in the mean rating of change from baseline were 0.37 units. The mean rating for the 24-32 mg/day group was statistically significantly superior to placebo.

Figure 12: Distribution of CIBIC-plus Ratings at Week 13



Age, Gender and Race:

Patient's age, gender, or race did not predict clinical outcome of treatment.

Extended-Release Capsules

The efficacy of RAZADYNE® ER Extended-Release Capsules was studied in a randomized, double-blind, placebo-controlled trial which was 6 months in duration, and had an initial 4-week dose-escalation phase. In this trial, patients were assigned to one of 3 treatment groups: RAZADYNE® ER in a flexible dose of 16 to 24 mg once daily; RAZADYNE® Tablets in a flexible dose of 8 to 12 mg twice daily; and placebo. The primary efficacy measures in this study were the ADAS-cog and CIBIC-plus. On the protocol-specified primary efficacy analysis at Month 6, a statistically significant improvement favoring RAZADYNE® ER over placebo was seen for the ADAS-cog, but not for the CIBIC-plus. RAZADYNE® ER showed a statistically significant improvement when compared with placebo on the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale, a measure of function, and a secondary efficacy measure in this study. The effects of both RAZADYNE® ER Capsules and RAZADYNE® Tablets on the ADAS-cog, CIBIC-plus, and ADCS-ADL were similar in this study.

INDICATIONS AND USAGE

RAZADYNE® ER/RAZADYNE® (galantamine hydrobromide) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS

RAZADYNE® ER/RAZADYNE® (galantamine hydrobromide) is contraindicated in patients with known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulation.

WARNINGS

Anesthesia

Galantamine, as a cholinesterase inhibitor, is likely to exaggerate the neuromuscular blocking effects of succinylcholine-type and similar neuromuscular blocking agents during anesthesia.

Cardiovascular Conditions

Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and AV block. These actions may be particularly important to patients with supraventricular cardiac conduction disorders or to patients taking other drugs concomitantly that significantly slow heart rate. Postmarketing surveillance of marketed anticholinesterase inhibitors has shown, however, that bradycardia and all types of heart block have been reported in patients both with and without known underlying cardiac conduction abnormalities. Therefore all patients should be considered at risk for adverse effects on cardiac conduction.

In randomized controlled trials, bradycardia was reported more frequently in galantamine-treated patients than in placebo-treated patients, but was rarely severe and rarely led to treatment discontinuation. The overall frequency of this event was 2-3% for galantamine doses up to 24 mg/day compared with <1% for placebo. No increased incidence of heart block was observed at the recommended doses.

Patients treated with galantamine up to 24 mg/day using the recommended dosing schedule showed a dose-related increase in risk of syncope (placebo 0.7% [2/286]; 4 mg BID 0.4% [3/692]; 8 mg BID 1.3% [7/552]; 12 mg BID 2.2% [6/273]).

Gastrointestinal Conditions

Through their primary action, cholinomimetics may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, e.g., those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of RAZADYNE® (galantamine hydrobromide) have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

RAZADYNE® ER/RAZADYNE®, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting, diarrhea, anorexia, and weight loss (see ADVERSE REACTIONS).

Genitourinary

Although this was not observed in clinical trials with RAZADYNE® ER/RAZADYNE®, cholinomimetics may cause bladder outflow obstruction.

Neurological Conditions

Seizures: Cholinesterase inhibitors are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of Alzheimer's disease. In clinical trials, there was no increase in the incidence of convulsions with RAZADYNE® ER/RAZADYNE®, compared to placebo.

Pulmonary Conditions

Because of its cholinomimetic action, galantamine should be prescribed with care to patients with a history of severe asthma or obstructive pulmonary disease.

PRECAUTIONS

Information for Patients and Caregivers:

Caregivers should be instructed about the recommended dosage and administration of RAZADYNE® ER/RAZADYNE® (galantamine hydrobromide). RAZADYNE® ER Extended-Release Capsules should be administered once daily in the morning, preferably with food (although not required). RAZADYNE® Tablets and Oral Solution should be administered twice per day, preferably with the morning and evening meals. Dose escalation (dose increases) should follow a minimum of four weeks at prior dose.

Patients and caregivers should be advised that the most frequent adverse events associated with use of the drug can be minimized by following the recommended dosage and administration.

Patients and caregivers should be advised to ensure adequate fluid intake during treatment. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

Caregivers should be instructed in the correct procedure for administering RAZADYNE® Oral Solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering RAZADYNE® Oral Solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

Deaths in Subjects with Mild Cognitive Impairment (MCI)

In two randomized placebo controlled trials of 2 years duration in subjects with mild cognitive impairment (MCI), a total of 13 subjects on RAZADYNE® (n=1026) and 1 subject on placebo (n=1022) died. The deaths were due to various causes which could be expected in an elderly population; about half of the RAZADYNE® deaths appeared to result from various vascular causes (myocardial infarction, stroke, and sudden death).

Although the difference in mortality between RAZADYNE® and placebo-treated groups in these two studies was significant, the results are highly discrepant with other studies of RAZADYNE®. Specifically, in these two MCI studies, the mortality rate in the placebo-treated subjects was markedly lower than the rate in placebo-treated patients in trials of RAZADYNE® in Alzheimer's disease or other dementias (0.7 per 1000 person years compared to 22-61 per 1000 person years, respectively). Although the mortality rate in the RAZADYNE®-treated MCI subjects was also lower than that observed in RAZADYNE®-treated patients in Alzheimer's disease and other dementia trials (10.2 per 1000 person years compared to 23-31 per 1000 person years, respectively), the relative difference was much less. When the Alzheimer's disease and other dementia studies were pooled (n=6000), the mortality rate in the placebo group numerically exceeded that in the RAZADYNE® group. Furthermore, in the MCI studies, no subjects in the placebo group died after 6 months, a highly unexpected finding in this population.

Individuals with mild cognitive impairment demonstrate isolated memory impairment greater than expected for their age and education, but do not meet current diagnostic criteria for Alzheimer's disease.

Special Populations

Hepatic Impairment

In patients with moderately impaired hepatic function, dose titration should proceed cautiously (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). The use of RAZADYNE® in patients with severe hepatic impairment is not recommended.

Renal Impairment

In patients with moderately impaired renal function, dose titration should proceed cautiously (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). In patients with severely impaired renal function (Cl_{cr} < 9 mL/min) the use of RAZADYNE® is not recommended.

Drug-Drug Interactions (see also CLINICAL PHARMACOLOGY, Drug-Drug Interactions)

Use With Anticholinergics

RAZADYNE® has the potential to interfere with the activity of anticholinergic medications.

Use With Cholinomimetics and Other Cholinesterase Inhibitors

A synergistic effect is expected when cholinesterase inhibitors are given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

A) Effect of Other Drugs on Galantamine

In vitro

CYP3A4 and CYP2D6 are the major enzymes involved in the metabolism of galantamine. CYP3A4 mediates the formation of galantamine-N-oxide; CYP2D6 leads to the formation of O-desmethyl-galantamine. Because galantamine is also glucuronidated and excreted unchanged, no single pathway appears predominant.

In vivo

Cimetidine and Ranitidine: Galantamine was administered as a single dose of 4 mg on day 2 of a 3-day treatment with either cimetidine (800 mg daily) or ranitidine (300 mg daily). Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the PK of galantamine.

Ketoconazole: Ketoconazole, a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, at a dose of 200 mg BID for 4 days, increased the AUC of galantamine by 30%.

Erythromycin: Erythromycin, a moderate inhibitor of CYP3A4 at a dose of 500 mg OID for 4 days, affected the AUC of galantamine minimally (10% increase).

Paroxetine: Paroxetine, a strong inhibitor of CYP2D6, at 20 mg/day for 16 days, increased the oral bioavailability of galantamine by about 40%.

Memantine: Memantine, an N-methyl-D-aspartate receptor antagonist, at a dose of 10 mg BID, had no effect on the pharmacokinetics of galantamine (16 mg/day) at steady state.

B) Effect of Galantamine on Other Drugs

In vitro

Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low.

In vivo

Warfarin: Galantamine at 24 mg/day had no effect on the pharmacokinetics of R- and S-warfarin (25 mg single dose) or on the prothrombin time. The protein binding of warfarin was unaffected by galantamine.

Digoxin: Galantamine at 24 mg/day had no effect on the steady-state pharmacokinetics of digoxin (0.375 mg once daily) when they were coadministered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia.

Carcinogenesis, Mutagenesis and Impairment of Fertility

In a 24-month oral carcinogenicity study in rats, a slight increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis or 6 times on an exposure [AUC] basis) and 30 mg/kg/day (12 times MRHD on a mg/m² basis or 19 times on an AUC basis). No increase in neoplastic changes was observed in females at 2.5 mg/kg/day (equivalent to the MRHD on a mg/m² basis or 2 times on an AUC basis) or in males up to the highest dose tested of 30 mg/kg/day (12 times the MRHD on a mg/m² and AUC basis).

Galantamine was not carcinogenic in a 6-month oral carcinogenicity study in transgenic (P 53-deficient) mice up to 20 mg/kg/day, or in a 24-month oral carcinogenicity study in male and female mice up to 10 mg/kg/day (2 times the MRHD on a mg/m² basis and equivalent on an AUC basis).

Galantamine produced no evidence of genotoxic potential when evaluated in the *in vitro* Ames *S. typhimurium* or *E. coli* reverse mutation assay, *in vitro* mouse lymphoma assay, *in vivo* micronucleus test in mice, or *in vitro* chromosome aberration assay in Chinese hamster ovary cells.

No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m² basis) for 14 days prior to mating in females and for 60 days prior to mating in males.

Pregnancy

Pregnancy Category B: In a study in which rats were dosed from day 14 (females) or day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m² basis) during the period of organogenesis.

There are no adequate and well-controlled studies of RAZADYNE® in pregnant women. RAZADYNE® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether galantamine is excreted in human breast milk. RAZADYNE® has no indication for use in nursing mothers.

Pediatric Use

There are no adequate and well-controlled trials documenting the safety and efficacy of galantamine in any illness occurring in children. Therefore, use of RAZADYNE® in children is not recommended.

ADVERSE REACTIONS

Pre-Marketing Clinical Trial Experience:

The specific adverse event data described in this section are based on studies of the immediate-release tablet formulation. In clinical trials, once-daily treatment with RAZADYNE® ER (galantamine hydrobromide) Extended-Release Capsules was well tolerated and adverse events were similar to those seen with RAZADYNE® Tablets.

Adverse Events Leading to Discontinuation:

In two large scale, placebo-controlled trials of 6 months duration in which patients were titrated weekly from 8 to 16 to 24, and to 32 mg/day, the risk of discontinuation because of an adverse event in the galantamine group exceeded that in the placebo group by about threefold. In contrast, in a 5-month trial with escalation of the dose by 8 mg/day every 4 weeks, the overall risk of discontinuation because of an adverse event was 7%, 7%, and 10% for the placebo, galantamine 16 mg/day, and galantamine 24 mg/day groups, respectively, with gastrointestinal adverse effects the principle reason for discontinuing galantamine. Table 1 shows the most frequent adverse events leading to discontinuation in this study.

Table 1: Most Frequent Adverse Events Leading to Discontinuation in a Placebo-Controlled, Double-Blind Trial With a 4-Week Dose Escalation Schedule

	4-Week Escalation		
Adverse Event	Placebo N=286	16 mg/day N=279	24 mg/day N=273
Nausea	<1%	2%	4%
Vomiting	0%	1%	3%
Anorexia	<1%	1%	<1%
Dizziness	<1%	2%	1%
Syncope	0%	0%	1%

Adverse Events Reported in Controlled Trials:

The reported adverse events in trials using RAZADYNE® (galantamine hydrobromide) Tablets reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ.

The majority of these adverse events occurred during the dose-escalation period. In those patients who experienced the most frequent adverse event, nausea, the median duration of the nausea was 5-7 days.

Administration of RAZADYNE® with food, the use of anti-emetic medication, and ensuring adequate fluid intake may reduce the impact of these events.

The most frequent adverse events, defined as those occurring at a frequency of at least 5% and at least twice the rate on placebo with the recommended maintenance dose of either 16 or 24 mg/day of RAZADYNE® under conditions of every 4-week dose-escalation for each dose increment of 8 mg/day, are shown in Table 2. These events were primarily gastrointestinal and tended to be less frequent with the 16 mg/day recommended initial maintenance dose.

Table 2: The Most Frequent Adverse Events in the Placebo-Controlled Trial With Dose Escalation Every 4 Weeks Occurring in at Least 5% of Patients Receiving RAZADYNE® and at Least Twice the Rate on Placebo.

Adverse Event	Placebo N=286	RAZADYNE® 16mg/day N=279	RAZADYNE® 24mg/day N=273
Nausea	5%	13%	17%
Vomiting	1%	6%	10%
Diarrhea	6%	12%	8%
Anorexia	3%	7%	9%
Weight decrease	1%	5%	5%

Table 3: The most common adverse events (adverse events occurring with an incidence of at least 2% with RAZADYNE® treatment and in which the incidence was greater than with placebo treatment) are listed in Table 3 for four placebo-controlled trials for patients treated with 16 or 24 mg/day of RAZADYNE®.

Table 3: Adverse Events Reported in at Least 2% of Patients With Alzheimer's Disease Administered RAZADYNE® and at a Frequency Greater Than With Placebo

Body System Adverse Event	Placebo (N=801)	RAZADYNE®[1] (N=1040)
Body as a whole - general disorders		
Fatigue	3%	5%
Syncope	1%	2%
Central & peripheral nervous system disorders		
Dizziness	6%	9%
Headache	5%	8%
Tremor	2%	3%
Gastrointestinal system disorders		
Nausea	9%	24%
Vomiting	4%	13%
Diarrhea	7%	9%
Abdominal pain	4%	5%
Dyspepsia	2%	5%
Heart rate and rhythm disorders		
Bradycardia	1%	2%
Metabolic and nutritional disorders		
Weight decrease	2%	7%
Psychiatric disorders		
Anorexia	3%	9%
Depression	5%	7%
Insomnia	4%	5%
Somnolence	3%	4%
Red blood cell disorders		
Anemia	2%	3%
Respiratory system disorders		
Rhinitis	3%	4%
Urinary system disorders		
Urinary tract infection	7%	8%
Hematuria	2%	3%

[1] Adverse events in patients treated with 16 or 24 mg/day of RAZADYNE® in four placebo-controlled trials are included.

Adverse events occurring with an incidence of at least 2% in placebo-treated patients that was either equal to or greater than with RAZADYNE® treatment were constipation, agitation, confusion, anxiety, hallucination, injury, back pain, peripheral edema, asthenia, chest pain, urinary incontinence, upper respiratory tract infection, bronchitis, coughing, hypertension, fall, and purpura.

There were no important differences in adverse event rates related to dose or sex. There were too few non-Caucasian patients to assess the effects of race on adverse event rates.

No clinically relevant abnormalities in laboratory values were observed.

Other Adverse Events Observed During Clinical Trials

RAZADYNE® Tablets were administered to 3055 patients with Alzheimer's disease. A total of 2357 patients received galantamine in placebo-controlled trials and 761 patients with Alzheimer's disease received galantamine 24 mg/day, the maximum recommended maintenance dose. About 1600 patients received galantamine for at least one year and approximately 200 patients received galantamine for two years.

To establish the rate of adverse events, data from all patients receiving any dose of galantamine in 8 placebo-controlled trials and 6 open-label extension trials were pooled. The methodology to gather and codify these adverse events was standardized across trials, using WHO terminology. All adverse events occurring in approximately 0.1% are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, or events unlikely to be drug caused. Events are classified by body system and listed using the following definitions: frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients; rare adverse events - those occurring in fewer than 1/1000 patients. These adverse events are not necessarily related to RAZADYNE® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. Additional adverse events observed in other clinical trials are also included below.

Body As a Whole – General Disorders: *Frequent:* chest pain, asthenia, fever, malaise

Cardiovascular System Disorders: *Infrequent:* postural hypotension, hypotension, dependent edema, cardiac failure, myocardial ischemia or infarction

Central & Peripheral Nervous System Disorders: *Infrequent:* vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia, leg cramps, tinnitus, transient ischemic attack or cerebrovascular accident

Gastrointestinal System Disorders: *Frequent:* flatulence; *Infrequent:* gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; *Rare:* esophageal perforation

Heart Rate & Rhythm Disorders: *Infrequent:* AV block, palpitation, atrial arrhythmias including atrial fibrillation and supraventricular tachycardia, QT prolonged, bundle branch block, T-wave inversion, ventricular tachycardia; *Rare:* severe bradycardia

Metabolic & Nutritional Disorders: *Infrequent:* hyperglycemia, alkaline phosphatase increased

Platelet, Bleeding & Clotting Disorders: *Infrequent:* purpura, epistaxis, thrombocytopenia

Psychiatric Disorders: *Infrequent:* apathy, paroniria, paranoid reaction, libido increased, delirium; *Rare:* suicidal ideation, suicide

Urinary System Disorders: *Frequent:* incontinence; *Infrequent:* hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi

Post-Marketing Experience:

Other adverse events from post-approval controlled and uncontrolled clinical trials and post-marketing experience observed in patients treated with RAZADYNE® include:

Body as a Whole – General Disorders: dehydration (including rare, severe cases leading to renal insufficiency and renal failure)

Psychiatric Disorders: aggression

Gastrointestinal System Disorders: upper and lower GI bleeding

Metabolic & Nutritional Disorders: hypokalemia

These adverse events may or may not be causally related to the drug.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug.

As in any case of overdose, general supportive measures should be utilized. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous system, and the neuromuscular junction. In addition to muscle weakness or fasciculations, some or all of the following signs of cholinergic crisis may develop: severe nausea, vomiting, gastrointestinal cramping, salivation, lacrimation, urination, defecation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

Tertiary anticholinergics such as atropine may be used as an antidote for RAZADYNE® (galantamine hydrobromide) overdosage. Intravenous atropine sulfate titrated to effect is recommended at an initial dose of 0.5 to 1.0 mg i.v. with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when coadministered with quaternary anticholinergics. It is not known whether RAZADYNE® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included hypoactivity, tremors, clonic convulsions, salivation, lacrimation, chromodacryorrhea, mucoid feces, and dyspnea.

In one postmarketing report, one patient who had been taking 4 mg of galantamine daily for a week inadvertently ingested eight 4 mg tablets (32 mg total) on a single day. Subsequently, she developed bradycardia, QT prolongation, ventricular tachycardia and torsades de pointes accompanied by a brief loss of consciousness for which she required hospital treatment. Two additional cases of accidental ingestion of 32 mg (nausea, vomiting, and dry mouth; nausea, vomiting, and substernal chest pain) and one of 40 mg (vomiting), resulted in brief hospitalizations for observation with full recovery. One patient, who was prescribed 24 mg/day and had a history of hallucinations over the previous two years, mistakenly received 24 mg twice daily for 34 days and developed hallucinations requiring hospitalization. Another patient, who was prescribed 16 mg/day of oral solution, inadvertently ingested 160 mg (40 mL) and experienced sweating, vomiting, bradycardia, and near-syncope one hour later, which necessitated hospital treatment. His symptoms resolved within 24 hours.

DOSAGE AND ADMINISTRATION

RAZADYNE® ER Extended-Release Capsules

The dosage of RAZADYNE® ER (galantamine hydrobromide) Extended-Release Capsules shown to be effective in a controlled clinical trial is 16-24 mg/day.

The recommended starting dose of RAZADYNE® ER is 8 mg/day. The dose should be increased to the initial maintenance dose of 16 mg/day after a minimum of 4 weeks. A further increase to 24 mg/day should be attempted after a minimum of 4 weeks at 16 mg/day. Dose increases should be based upon assessment of clinical benefit and tolerability of the previous dose.

RAZADYNE® ER should be administered once daily in the morning, preferably with food.

Patients currently being treated with RAZADYNE® tablets can convert to RAZADYNE® ER by taking their last dose of RAZADYNE® tablets in the evening and starting RAZADYNE® ER once daily treatment the next morning. Converting from RAZADYNE® to RAZADYNE® ER should occur at the same total daily dose.

RAZADYNE® Immediate-Release Tablets and Oral Solution

The dosage of RAZADYNE® Tablets shown to be effective in controlled clinical trials is 16-32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16-24 mg/day given in a BID regimen. The dose of 24 mg/day did not provide a statistically significant greater clinical benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg of RAZADYNE® might provide additional benefit for some patients.

The recommended starting dose of RAZADYNE® Tablets and Oral Solution is 4 mg twice a day (8 mg/day). The dose should be increased to the initial maintenance dose of 8 mg twice a day (16 mg/day) after a minimum of 4 weeks. A further increase to 12 mg twice a day (24 mg/day) should be attempted after a minimum of 4 weeks at 8 mg twice a day (16 mg/day). Dose increases should be based upon assessment of clinical benefit and tolerability of the previous dose. RAZADYNE® Tablets and Oral Solution should be administered twice a day, preferably with morning and evening meals.

Patients and caregivers should be advised to ensure adequate fluid intake during treatment. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

Caregivers should be instructed in the correct procedure for administering RAZADYNE® Oral Solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering RAZADYNE® Oral Solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

The abrupt withdrawal of RAZADYNE® ER/RAZADYNE® in those patients who had been receiving doses in the effective range was not associated with an increased frequency of adverse events in comparison with those continuing to receive the same doses of that drug. The beneficial effects of RAZADYNE® ER/RAZADYNE® are lost, however, when the drug is discontinued.

Doses in Special Populations

Galantamine plasma concentrations may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), the total daily dose should generally not exceed 16 mg/day. The use of RAZADYNE® ER/RAZADYNE® in patients with severe hepatic impairment (Child-Pugh score of 10-15) is not recommended.

For patients with moderate renal impairment the dose should generally not exceed 16 mg/day. In patients with severe renal impairment (creatinine clearance <9 mL/min), the use of RAZADYNE® ER/RAZADYNE® is not recommended.

HOW SUPPLIED

RAZADYNE® ER (galantamine hydrobromide) Extended-Release Capsules contain white to off-white pellets.

8 mg white opaque, size 4 hard gelatin capsules with the inscription "GAL 8."

16 mg pink opaque, size 2 hard gelatin capsules with the inscription "GAL 16."

24 mg caramel opaque, size 1 hard gelatin capsules with the inscription "GAL 24."

The capsules are supplied as follows:

8 mg capsules – bottles of 30 NDC 50458-387-30

16 mg capsules – bottles of 30 NDC 50458-388-30

24 mg capsules – bottles of 30 NDC 50458-389-30

RAZADYNE® Tablets are imprinted "JANSSEN" on one side, and "G" and the strength "4", "8", or "12" on the other.

4 mg off-white tablet: bottles of 60 NDC 50458-396-60

8 mg pink tablet: bottles of 60 NDC 50458-397-60

12 mg orange-brown tablet: bottles of 60 NDC 50458-398-60

RAZADYNE® 4 mg/mL oral solution (NDC 50458-490-10) is a clear colorless solution supplied in 100 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.5 mL, while the maximum calibrated volume is 4 mL.

Storage and Handling

RAZADYNE® ER Extended-Release Capsules should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

RAZADYNE® Tablets should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

RAZADYNE® Oral Solution should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. DO NOT FREEZE.

Keep out of reach of children.

RAZADYNE® ER Extended-Release Capsules and RAZADYNE® Tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico

RAZADYNE® Oral Solution is manufactured by: Janssen Pharmaceutica N.V., Beerse, Belgium

RAZADYNE® ER Extended-Release Capsules and RAZADYNE® Tablets and Oral Solution are distributed by: ORTHO-McNEIL NEUROLOGICS, INC., Titusville, NJ 08560

7517314 Revised August 2006 US Patent No. 4,663,318 © OMN 2005

ORTHO-McNEIL NEUROLOGICS, INC.

01R2291A

EXHIBIT 69

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
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MEMORANDUM

DATE: **May 3, 2007**

TO: **Technology Center Directors**

FROM: **Margaret A. Focarino**
Deputy Commissioner
for Patent Operations

SUBJECT: **Supreme Court decision on *KSR Int'l. Co., v. Teleflex, Inc.***

The Supreme Court has issued its opinion in *KSR*, regarding the issue of obviousness under 35 U.S.C. § 103(a) when the claim recites a combination of elements of the prior art. *KSR Int'l Co. v. Teleflex, Inc.*, No 04-1350 (U.S. Apr. 30, 2007). A copy of the decision is available at http://www.supremecourtus.gov/opinions/06pdf/04-1350.pdf. The Office is studying the opinion and will issue guidance to the patent examining corps in view of the *KSR* decision in the near future. Until the guidance is issued, the following points should be noted:

(1) The Court reaffirmed the *Graham* factors in the determination of obviousness under 35 U.S.C. § 103(a). The four factual inquiries under *Graham* are:

(a) determining the scope and contents of the prior art;
(b) ascertaining the differences between the prior art and the claims in issue;
(c) resolving the level of ordinary skill in the pertinent art; and
(d) evaluating evidence of secondary consideration.

Graham v. John Deere, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966).

(2) The Court did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

(3) The Court rejected a rigid application of the "teaching, suggestion, or motivation" (TSM) test, which required a showing of some teaching, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the prior art elements in the manner claimed in the application or patent before holding the claimed subject matter to be obvious.

(4) The Court noted that the analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit, and that it was "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. The Court specifically stated:

> Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an **apparent reason** to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis **should be made explicit.**

KSR, slip op. at 14 (emphasis added).

Therefore, in formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

CERTIFICATE OF SERVICE

I hereby certify that on the 30th day of August, 2007, the attached **REDACTED PUBLIC VERSION OF APPENDIX III: TRIAL EXHIBITS AND ADDITIONAL AUTHORITIES** was served upon the below-named counsel of record at the address and in the manner indicated:

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